SEPTEMBER 1953
VOL. VIII NO. 3

Circulation

JOURNAL of the AMERICAN HEART ASSOCIATION

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Circulation
A Journal of the American Heart Association

SEPTEMBER 1953
VOL. VIII NO. 3

Mitral Commissurotomy in the Older Aged Patient

An Analysis of Twenty Patients Over the Age of Fifty

By O. Henry Janton, M.D., Robert P. Glover, M.D., and Thomas J. E. O'Neill, M.D.

An analysis of 20 consecutive cases of mitral stenosis (from a total of 400 cases) in patients between the ages of 50 and 61 treated by mitral commissurotomy from May 1951, to October 1952, is presented. The data suggests that the patient over 50 with symptomatic mitral stenosis can have a functionally satisfactory commissurotomy performed without undue operative risk and with essentially the same ultimate degree of improvement enjoyed by patients requiring treatment at an earlier age.

PREVIOUS communications on the surgical treatment for mitral stenosis have reviewed its historical development, surgical technics, the indications for and results of mitral commissurotomy.[1-13] Mitral commissurotomy is briefly defined as the direct surgical approach through the left auricular appendage for the correction of mitral stenosis by separating the individual anatomic leaflets of the mitral valve. Incision of the angles or commissures of the stenosed mitral orifice frequently re-establishes function of the valve leaflets without producing significant mitral insufficiency. Hence, the purpose of the procedure is three-fold: (1) to enlarge the constricted orifice, (2) to restore motion to the valve leaflets, and (3) to prevent future arterial embolization by eliminating the source of the thrombus and/or by reducing stasis in the left auricle.

The purpose of this communication is to present the results in 20 patients between the ages of 50 and 61 (out of a total 400 consecutive cases) subjected to mitral commissurotomy. These patients have been followed for six months to two years. It will be shown that in selected patients over the age of 50 years intracardiac surgery can be performed without unusual morbidity or mortality, and significant improvement in functional capacity can be expected despite the chronologic age.

Analysis of Cases

Twenty patients whose ages ranged from 50 to 61 years were subjected to mitral commissurotomy between May 4, 1951, and Oct. 11, 1952. Eleven of these were female and nine were male. The oldest was a man aged 61, one patient was 57, one 55, three 54, five 53, four 52, two 51 and three were 50 years of age. All of these patients were markedly incapacitated; 17 were placed in the functional class III and three were placed in class IV.[16]

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Read by title at the Scientific Sessions of the Twenty-Sixth Annual Meeting of the American Heart Association, Atlantic City, N. J., April 9–12, 1953.

Status Prior to Admission (table 1)

A definite history of rheumatic fever and/or chorea was obtained in only eight of these patients; in these eight patients the initial infection occurred in childhood. It is interesting that in this small group symptoms appeared in the later decades of life rather than in childhood or youth which was the common finding in our total series of 400 patients who were operated upon. This long interval between the initial rheumatic infection and the occurrence of symptoms points out that a significant number of people having the *murmur* of mitral stenosis live a normal, productive life for many years and possibly in rare instances may live a normal life span. However, for those who do become incapacitated, even though they be in the geriatric age group, mitral valve surgery is indicated and should not be withheld merely because of age.

TABLE 1.—*Status Prior to Admission*

History of rheumatic infection	8
Progressive functional incapacity	20
Recurrent hemoptyses	3
Minimal to marked congestive failure	18
Systemic arterial embolism	5

All of the patients had progressive cardiopulmonary embarrassment. Slight activity produced severe dyspnea in each, and in three there were recurrent severe hemoptyses.

Eighteen had had one or more bouts of acute congestive heart failure, and three of these had been in chronic right heart failure for one to three years before they were operated upon. The latter three were considered desperate risks in view of the marked cardiomegaly, the poor response to a strict antifailure medical regime and persistent hepatomegaly of marked degree.

Systemic embolic episodes had occurred on one or more occasions in five patients. Four of these five patients had cerebral emboli in addition to emboli to the abdomen or legs. The only residual findings in these patients were incoordination of the finer movements of the fingers in three, and in one a right lateral homonymous hemianopsia. One other patient had had a suspected saddle embolus in May 1950, but vascular exploration failed to reveal the embolus. This patient had had severe, bilateral intermittent claudication since this episode. The longest time interval between the date of the first arterial embolism and commissurotomy was 17 years and occurred in a patient who had had a cerebral embolus in 1935 and a similar episode in 1936 and 1937, his only residual finding on admission being a right lateral homonymous hemianopsia. The shortest interval was two years in the patient with a possible saddle embolus. The other three patients had their vascular accidents from two to three and one-half years prior to commissurotomy. All of these five patients were in permanent auricular fibrillation on admission, and through the cooperation of the referring physicians it was established that auricular fibrillation in four had been present at the time of their vascular insults. Interestingly, four of these five patients had a thrombus in the left auricular appendage and/or the left auricle at operation, but in one the left heart chambers did not disclose a thrombus to the examining finger. At the present writing none of these five patients has had recurrences of their embolic episodes.

Admission Findings (table 2)

The preoperative valvular lesions diagnosed were "pure" mitral stenosis in 11 patients and there was a mitral stenosis and associated mitral insufficiency in nine. One patient had been diagnosed as having a possible aortic insufficiency in addition to the mitral valve lesion because of a grade II diastolic blowing murmur heard at the second and third left intercostal spaces at the parasternal line. This murmur disappeared after operation, indicating that the murmur was a functional pulmonic diastolic murmur so brilliantly described by Graham Steell in 1888.[17] In a previous communication[11] one of us (O.H.J.) pointed out that this murmur was present in 6 of the first 100 patients undergoing commissurotomy, and in all such instances, including the patient in this series, the main pulmonary arteries were found to be enormously dilated and tense during the operation. Mitral insufficiency

associated with mitral stenosis was considered dynamic if the left ventricle was enlarged and adynamic if this chamber was of normal size. The left ventricle was considered to be slightly enlarged in two of the nine patients with mitral stenosis and insufficiency. At operation, with the finger in the left auricle a systolic regurgitant jet was felt in all nine patients. This is not the usual finding in our larger series of cases, where a preoperative diagnosis of mitral insufficiency was not always confirmed by the operative demonstration of a systolic regurgitant jet at surgery. This is to be expected in view of the manipulation and possible arrhythmias occurring during intracardiac manipulation with consequent reduction in the force of ventricular systole.

In selection of cases for surgery the clinical recognition of a typical mitral stenosis usually presents no problem. However, in patients with coexisting mitral insufficiency and/or aortic valvular disease the diagnosis of mitral stenosis as the predominant lesion may be perplexing. In such cases, the greatest aid in our hands has been fluoroscopic and roentgenologic examination of cardiac chamber size. Radiologic estimation of right ventricular and left auricular enlargement seems reasonably accurate. Our most difficult problem has been estimating left ventricular enlargement in the presence of a markedly enlarged right ventricle. Posterior displacement and rotation of a normal left ventricle by an enlarged right ventricle are well known.[15] In addition to the left ventricle being displaced posteriorly by the enlarged right ventricle, marked enlargement of the left auricle may form variable portions of the lower left cardiac border in the left anterior oblique projection. In 1 of our 20 patients the left auricle extended downward and intruded into the posterior inferior cardiac recess and simulated the obliteration of this space commonly seen in left ventricular enlargement. At operation this patient was found to have, in addition to the marked enlargement of the right ventricle, massive dilatation of the left auricle. Our most reliable single guide in assessing the size of the left ventricle has been the position of the cardiac "apex" in frontal projection which has been pointed out by Lehman and others.[14] When this position of the cardiac apex is not definable and if the posterior inferior cardiac recess is obliterated, we are unable to predict the size of the left ventricle. In such instances we feel cardiac catheterization is indicated and helpful.

Preoperative right ventricular and left auricular enlargement was recorded as *marked* in four patients. In two of these the left ventricle was also thought to have been slightly enlarged. At operation these findings were corroborated and, in addition, an aneurysmal enlargement of the left auricle was found in one. The remaining 16 patients had moderate

TABLE 2.—*Findings on Admission*

"Pure" mitral stenosis		11
Mitral stenosis with associated insufficiency		9
a. Adynamic mitral insufficiency		7
b. Dynamic mitral insufficiency		2
Cardiac enlargement (x-ray)		20
a. Left auricle, moderate to marked		20
b. Right ventricle	marked	4
	moderate	16
c. Left ventricular enlargement, minimal		2
Auricular Fibrillation		12
Electrocardiogram	R.A.D.	15
	N.A.D.	4
	L.B.B.B.	1
Functional Classification	Class III	17
	Class IV	3

right ventricular and left auricular enlargement without associated enlargement of the left ventricle.

Calcification diagnosed before operation was confirmed at operation in 10 patients, and in an additional three patients calcification about the cicatricial mitral orifice not recognized preoperatively was found by the surgeon.

Three patients were in chronic congestive heart failure of one to three years' duration. All three patients had marked cardiac chamber enlargement and auricular fibrillation.

Permanent auricular fibrillation was present in 12, all of whom had electrocardiographic evidence of right ventricular hypertrophy as did three patients with normal sinus rhythm. The electrocardiogram in four patients revealed a normal electrical axis without evidence of right ventricular enlargement. In one,

auricular fibrillation with a complete left bundle branch block was present. In this latter case a successful commissurotomy was performed without any change postoperatively in the electrocardiographic pattern. It has been our experience that the presence of an abnormal left axis deviation or a combined strain pattern is probably a contraindication to mitral commissurotomy.

Operative Findings (fig. 1)

A thrombus was found at surgery in four of the five patients with a preoperative history of arterial embolic episodes. Five other patients

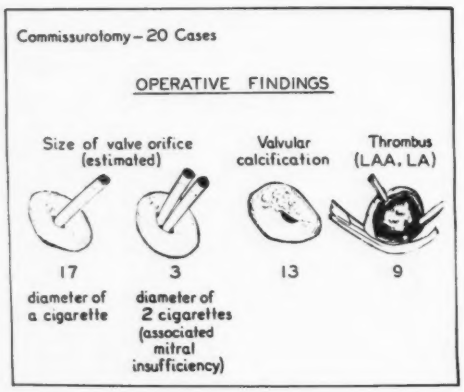

FIG. 1

also had thrombi, making a total of nine patients in whom a thrombus in the left auricular appendage and/or left auricle was found. In seven the clot appeared to be contained in the appendage and was removed by auricular appendectomy. In two the clot was also present in the auricle as well as the appendage. Strikingly, only one of these nine patients suffered an operative embolic insult.

The size of the valve orifice as estimated by the examining index finger was less than 1 cm. in diameter (diameter of a cigarette) in 17 instances and was slightly larger in three. The cusp margins were thickened and indurated and the valve leaflets themselves varied in consistency from that of kid glove to that of heavy shoe leather. The chordae tendineae were foreshortened, thickened and matted together in all patients. In five these changes were so marked that the valvular diaphragm was rigid and completely fixed, all semblance of a functioning valve being lost; in the remaining 15 varying degrees of flexibility were present.

Calcification was present in varying amount in 13 of the 20 valves. In five it was excessive, infiltrating the valve leaflets and thereby constituting the major cause for complete fixation of the valve as mentioned above. In the remaining eight, the calcium varied from tiny, sand-like calcific beads along the cusp margin to complete encirclement of the valve orifice with extension into the valve leaflets. The most frequent site and position of maximum deposition of calcium was on the anterior valve leaflet at its medial aspect, that part nearest the left ventricular outflow tract.

TABLE 3.—*Present Functional Status*

Excellent	6
Improved	9
Unimproved	3
Deaths	
a. operative	0
b. late (class IV)	2
	20

Despite the advanced nature of the valvular pathology, in 12 it was possible to successfully and ideally separate the valve leaflets to a width of 3.0 to 4.0 cm. (sufficient to admit two fingers). In the remaining eight the opening was satisfactory from a functional standpoint, although the mitral vent in seven could only be enlarged to 2.5 cm. (one to one and one-half fingers) and opened to 1.5 to 2.0 cm. (one finger) in one other. In none of the cases was a clinically significant insufficiency produced, even in those who had minimal insufficiency prior to commissurotomy.

RESULTS AND DISCUSSION (TABLE 3)

I. Immediate Postoperative Status

It is realized that this small number of patients is of little statistical importance. However, it was unexpected to find so little difference in the postoperative complications

and functional results from those found in the younger age group.

It was interesting to note that the eight patients in this geriatric group with normal sinus rhythm did not develop cardiac arrhythmias postoperatively, as compared with the reported incidence of 15 per cent occurring in our first 100 patients.[11]

Two patients awoke from anesthesia with evidence of having suffered a cerebrovascular accident; another had sudden severe left calf pain four hours after surgery. One of these patients developed a left hemiplegia. At present, 16 months after surgery, all faculties have returned to normal except that there is some loss of coordination of the finer movements of the fingers. Unfortunately, the other patient developed an incomplete motor aphasia with agraphia and inability to comprehend written and printed speech. Verbal speech comprehension was affected but slightly. Although his functional status has improved considerably, the aphasia remains. The third patient, who developed severe pain in the left calf, about four hours after surgery, had a preoperative history of frequent embolic episodes to the brain, viscera and extremities. An embolectomy in the right femoral artery had been attempted in 1948, and since that time she had had bilateral intermittent claudication. Pulses in the dorsalis pedi and popliteal arteries were not palpable before commissurotomy. She was placed on Dicumarol after the embolectomy and remained on this drug up to one week prior to surgery. A thrombus in the auricular appendage was removed and a successful commissurotomy performed. She moved all four extremities immediately postoperatively, and no indication of a vascular injury was apparent until four hours later, when sudden pain was noted in the left leg. A therapeutic caudal block was started without appreciable effect during the following 48 hours. The left leg remained cool, and marked mottling with subsequent demarcation just below the knee developed. An exploration of the left femoral artery revealed a good but not pulsatile flow of blood, and no embolus could be located from the aortic bifurcation to the popliteal artery. Finally a left midthigh amputation was done with an excellent recovery. Careful examination of the vascular tree of the amputated limb failed to reveal any embolus, and it was considered that the changes noted in all the vessels could be attributed to thromboangiitis obliterans.

II. Present Functional Status

It is stressed again that there was no increase in morbidity in these patients, the average postoperative hospital time being 15 days. With the exception of the one patient who had undergone amputation of the left leg, all of the patients were discharged from the hospital between 10 and 21 days after surgery. There has been no reactivation of rheumatic infection, and there has been no recurrence of hemoptyses or embolic phenomena.

The operative results in six patients are classified as being excellent, they having returned to a normal productive life compatible with their age group without obvious cardiac disability. These patients are carried on a maintenance dose of digitalis, and, even though they have progressively increased their activity, there has been no necessity for excessive salt restriction or the use of mercurial diuretics. Nine are felt to be objectively and subjectively improved as evidenced by their resumption of almost normal activity. These patients, in addition to the daily digitalis, have remained on a low sodium diet and on occasion mercurial diuretics have been used. Their progressive downhill course has been successfully terminated or reversed, some to gain a high level of efficiency and others to remain on an improved plateau.

Three of the 20 patients have not been essentially improved by the operation. One of these had a dynamic mitral insufficiency and marked right ventricular enlargement. The valve of another was fixed and heavily calcified so that adequate separation of the valve leaflets was impossible. The third should have had a satisfactory result, based on the condition of her valve and the presence of only moderate ventricular enlargement, but she refused to follow the instructions of her physician which has immeasurably delayed, perhaps permanently, a beneficial response.

The remaining two cases have died three months and eight months after commissurotomy. Before operation both had been in chronic congestive heart failure for over two years with marked hepatomegaly and marked cardiomegaly. In one, auricular fibrillation had been present for over four years, and in the other a normal sinus rhythm was present. It was striking that these two patients during the immediate postoperative state appeared to have improved. However, with increased physical activity, irreversible congestive heart failure resulted even though a technically satisfactory commissurotomy was performed.

If there is one outstanding prognostic factor, it is felt that cardiac size is the most decisive indicator of future surgical benefits. With a technically satisfactory commissurotomy, the greatest benefits result in those patients with only slight to moderate right ventricular enlargement. The least, or no improvement at all, is to be expected in patients with tremendous cardiac enlargement of the right ventricle and especially if this is associated with enlargement of the left ventricle and/or massive dilatation of the left auricle. Two of the four patients with marked right ventricular enlargement died in congestive heart failure and one other has been unimproved. The remaining patient has slowly and progressively improved his functional status. Generally, it is felt that marked right ventricular enlargement is a serious prognostic factor. In such instances the myocardium is so severely damaged that there is a poor functional response even with adequate valvular surgery.

In the cases presented here, as well as in the total 400 patients, an unexpected finding has been the constancy of the size of the stenotic mitral valve inlet. Whether the symptoms be minimal or marked and of long duration, the orifice has rarely varied in diameter from 0.5 to 1.0 cm. or, in more easily appreciated terms, the head of a paper match to one cigarette.

We feel that there is a "critical point" of orificial contraction at which time symptoms appear, and thereafter little change in the diameter of the valvular opening takes place. This is in contrast to the progressive pathologic changes in the valve leaflets, chordae tendineae and papillary muscles, which roughly parallel the stage and duration of the disease. It appeals to us that if this is true, much of the success of the commissurotomy lies in recognizing *when* this "critical point of contraction" is reached. It is at this time, when progressive symptoms first develop, that the valve offers the best opportunity for maximal functional restoration.

Summary

Twenty patients over the age of 50 in whom mitral commissurotomy was performed have been presented in detail. Fifteen have benefited significantly from their surgery and therefore justified operative intervention. Morbidity and mortality are comparable with that seen in the younger age group, therefore such patients should not be denied surgery because of the factor of chronologic age alone.

Addendum

To date the total number of cases in this series has reached 35 with an operative mortality of 8.5 per cent (three deaths).

Sumario Español

Un analisis de 20 casos consecutivos de estenosis mitral (de un total de 400 casos) en pacientes entre las edades de 50 a 61 tratados con comisurotomía mitral desde Mayo, 1951, a Octubre, 1952, se presenta. Los datos sugieren que los pacientes sobre 50 con estenosis mitral sintomática pueden sufrir una comisurotomía con resultados funcionalmente satisfactorios sin riesgo excesivo operatorio y con esencialmente el mismo grado de mejora gozado por pacientes que requieren la operación a una más temprana edad.

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Tetralogy of Fallot with Unilateral Pulmonary Atresia

A Clinically Diagnosable and Surgically Significant Variant

By Alexander S. Nadas, M.D., Harold D. Rosenbaum, M.D., Martin H. Wittenborg, M.D., and Abraham M. Rudolph, M.D.

Four patients with tetralogy of Fallot syndrome, whose physical and x-ray findings were distinctly unusual, are presented in this report. All these patients were demonstrated to have functional or anatomic atresia of one of the main pulmonary arteries, in addition to the characteristic features of the tetralogy of Fallot. Diagnostic criteria, including angiocardiograms, are presented, and the therapeutic implications are discussed.

SINCE the report by Blalock and Taussig[1] in 1945 of the first successful "shunt operations" in three children with the tetralogy of Fallot syndrome, well over 1,000 such patients have been subjected to surgery throughout the United States.[2, 3]

The successful accomplishment of an aorto-pulmonary shunt in a patient with tetralogy of Fallot will depend to a large extent on the availability of a pulmonary artery through which systemic blood can be directed to the lungs and on the presence of a second vessel to maintain the pulmonary circulation during the period of temporary occlusion of the first pulmonary vessel.

In the majority of patients with tetralogy of Fallot, the diagnosis is made on clinical grounds alone. The history, physical examination, roentgenologic findings, and the electrocardiogram in the typical case represent a relatively easily identifiable entity. As has been pointed out by Taussig[4] and others, the presence and the size of the pulmonary arteries in the individual case may be quite difficult to assess clinically as well as by angiocardiography.

The purpose of this paper is to report four patients with tetralogy of Fallot in whom the unusual distribution of the pulmonary arteries makes surgical correction a very hazardous undertaking. Physical and radiologic signs make this a well recognizable clinical entity.

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Case Reports

The individual case reports are given below, with the salient points summarized in table 1.

Case 1. J. D. (no. 356134) was the product of an uneventful pregnancy and delivery. Cyanosis and labored respirations appeared six hours after birth and persisted despite administration of oxygen. Feedings were taken poorly, and frequent suctioning of the oropharynx was necessary because of excessive mucus.

Physical examination revealed a moderately cyanotic male infant in no acute distress. Temperature was 99.4 F., pulse rate 116, respirations 48 per minute, and blood pressure 84 (systolic). There was no clubbing of the fingers, deformity of the chest, distention of neck veins, or peripheral edema. Femoral and radial pulses were equal and strong. The liver extended 2 cm. below the right costal margin in the nipple line. No thrills were felt. A grade IV, rough systolic murmur was heard all over both sides of the chest. The murmur was loudest over the right upper chest anteriorly.

The hemoglobin was 17 Gm. per 100 ml., the erythrocyte count 5.6 million per cubic millimeter, and the hematocrit 52 per cent. The electrocardiogram showed right axis deviation and right ventricular hypertrophy.

Films and fluoroscopic examination of the chest revealed a considerable shift of the heart and mediastinum to the left, obscuring most of the left lung. The right upper and middle lobes appeared emphysematous, and the right lower lobe was collapsed. The right hilum contained a large conglomerate area of increased density, some portions of which were rounded and suggested a

vascular structure. The heart was not significantly enlarged, but the right ventricle was prominent.

A bronchogram, taken because of the evidence of obstruction of air exchange to the right lung, showed normal bronchi on the left, but flow of the opaque medium into the right lung was almost completely obstructed at the bifurcation of the right main bronchus by the rounded hilar densities previously described (fig. 1). These hilar masses appeared on angiocardiography to be vascular (fig. 2), suggesting the possibility of an arteriovenous malformation in this area. No left pulmonary artery could be demonstrated on the films. There was overriding of the aorta with a right aortic arch, and the thoracic aorta descended on the right.

be calculated to be 4 mm. or less in diameter. No pulmonic cusps were present. In their stead were several tiny greyish-white granular elevations. *The pulmonary artery passed directly to the right hilum without there being any left pulmonary artery at all. In the right hilum the pulmonary artery rapidly dilated into a thin-walled sac which measured 3.2 cm. in circumference.* Several branches passed from this aneurysmal right pulmonary artery into the right lung. The only blood supply to the left lung was a tiny branch of the innominate artery which passed into this lung just above the hilum. A high ventricular septal defect, measuring 0.7 cm. in diameter, was present. The aorta directly overrode this defect, and there was a right aortic arch and right descend-

TABLE I.—*Summary of Important Clinical and Laboratory Findings in Four Cases of Tetralogy of Fallot with Atresia of One Main Pulmonary Artery*

Case No.	Age Yrs.	Cyanosis	P_2*	Maximal Murmur	X-Ray Findings						ECG	Confirmed by		
					Right Ventricle	Pulmonary Artery		Pulmonary Vasculature		Aortic Arch		Cardiac Cath.	Angiocardiography	Autopsy
						Left	Right	Left	Right					
1	1/12	Yes	?	Systolic 2 RIS†	Enlarged	Absent	Large	−−	++	Right	RVH§	No	Yes	Yes
2	4½	Yes	Diminished	Systolic 2 RIS†	Enlarged	Atretic	Large	−−	++	Left	RVH§	Yes	Yes	No
3	3½	Yes	Diminished	Systolic 2 RIS†	Enlarged	Atretic	Large	−−	++	Left	RVH§	Yes	Yes	No
4	3¼	Yes	Diminished	Systolic 2 LIS‡	Enlarged	Large	Atretic	++	−−	Right	Dextrocardia; ? RVH	Yes	Yes	No

* Pulmonic second sound.
† Second right intercostal space.
‡ Second left intercostal space.
§ Right ventricular hypertrophy.

Although it was felt that the patient suffered from congenital heart disease, the possibility of an arteriovenous aneurysm, in addition, compressing the right main bronchus, seemed to warrant a right exploratory thoracotomy. At operation, an aneurysmal mass was present in the right hilum. A thrill was felt throughout the right lung and especially strongly over the hilar mass. This thrill disappeared on compression of the hilum. Such compression, however, caused a 10 to 20 per cent drop in blood oxygen saturation as indicated by an oximeter placed on the patient's ear. It was decided that the baby probably did not have sufficient oxygen uptake from his left lung to survive a right pneumonectomy. Consequently, the chest was closed.

Following surgery, respirations became increasingly rapid and labored, and cyanosis increased. Death occurred on the second postoperative day.

At *autopsy*, the heart was slightly enlarged, and the right ventricle was hypertrophied. The pulmonic ring was formed by a tough band of tissue only 1.6 cm. in circumference, and from this the orifice may

ing aorta. The ductus arteriosus was absent. No other abnormalities were present in the heart (fig. 3).

The right main stem bronchus was severely compressed between the aneurysmal right pulmonary artery and the right descending aorta. This led to the obstructive emphysema in the right upper and middle lobes and the collapse of the right lower lobe. The entire left lung was atelectatic and involved in a pneumonic process.

Case 2. T. H. (no. 352566). This white male, age 4 years and 8 months, was referred for study by a pediatrician who heard a "loud murmur" at the age of 3 months. Mild cyanosis, accentuated by exertion, appeared at 14 months of age. Shortness of breath on exertion appeared two years before admission, but these symptoms had not been incapacitating. There was no history of squatting, anoxic spells, epistaxis, hemoptysis, or evidence of congestive cardiac failure.

Physical examination revealed a well nourished boy, somewhat small for his age. Temperature was 99.6 F., pulse rate 100, respirations 20 per minute,

and blood pressure 92/52 (left arm). There was mild cyanosis of the lips, fingers, and toes, without clubbing. The neck veins were not distended, and there was no chest deformity or peripheral edema.

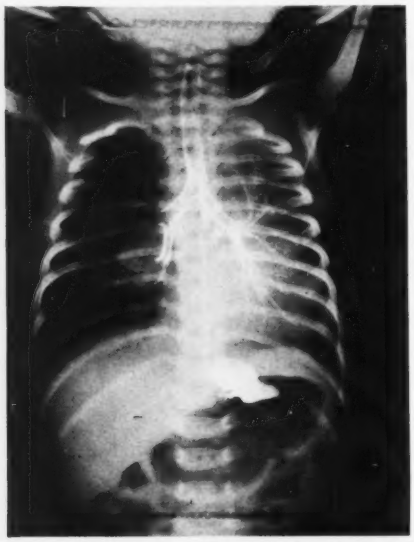


FIG. 1. Bronchogram of case 1. Note obstruction of right main bronchus by hilar densities.

murmur was best heard in the third left intercostal space near the sternum. There was *a second harsh systolic murmur, grade IV in intensity, loudest along the upper right sternal border.* This murmur radiated well to all of the right chest as well as to the right side of the neck.

Laboratory studies showed a hemoglobin of 14 Gm., an erythrocyte count of 8.0 million, and a hematocrit of 47 per cent. Circulation time, arm to tongue (fluorescein), was 8 seconds. The electrocardiogram showed right axis deviation and marked right ventricular hypertrophy.

Films and fluoroscopic examination of the chest showed a slight increase in the transverse diameter of the heart with definite enlargement of the right ventricle. The normal pulsation of the main pulmonary artery was not seen at fluoroscopy, but there was no concavity in the left upper portion of the cardiac silhouette. *The vascular markings in the right lung were considerably increased* and showed an active expansile pulsation. In contrast, *the vascular markings in the left lung were definitely diminished in caliber.* There was a left aortic arch.

An angiocardiogram showed simultaneous filling of the pulmonary artery and the aorta from the right ventricle. There was stenosis of the left pulmonary artery in the region of its bifurcation with very little, if any, contrast medium being visualized in the peripheral vessels of the left lung. The right pulmonary artery was dilated, and its peripheral

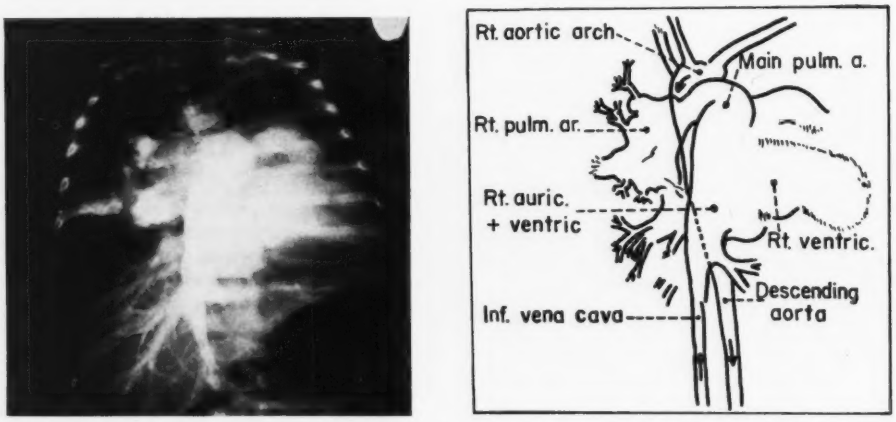


FIG. 2. Angiocardiogram of case 1. Hilar shadows seen in figure 1 are here filled with radiopaque substance, proving vascular nature of these structures. No left pulmonary artery is seen.

Femoral pulsations were strong. The liver extended 4 cm. below the right costal margin in the nipple line. The apex was in the fifth left intercostal space, 0.5 cm. beyond the midclavicular line. No thrills were felt. The second sound was diminished in the pulmonic area but was quite loud along the lower left sternal border. A grade III, rough systolic

branches were unusually large (fig. 4*a*). The left atrium filled by pulmonary veins leading from the right lung, with no vessels from the left lung being seen. The aorta was refilled from the left ventricle, proving the presence of overriding (fig. 4*b*).

At cardiac catheterization, the pressure in the pulmonary artery and its right branch was 18/7,

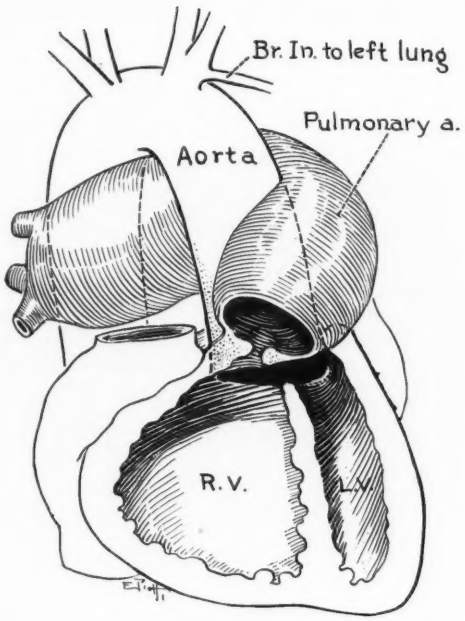
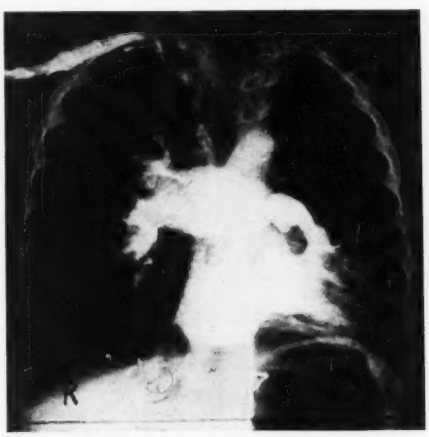


FIG. 3. Schematic presentation of autopsy findings in case 1. Note overriding aorta, ventricular septal defect, and pulmonic stenosis with large right main pulmonary artery. Left main pulmonary artery is absent.

of 83 per cent, a right-to-left shunt of 1.6 liters per square meter of body surface area per minute, and a left-to-right shunt of 0.7 liters per square meter of surface area per minute.

Case 3. R. S. (no. 341910). This 3½ year old white boy was the result of an uneventful pregnancy except that the mother had measles during the second month. The baby was cyanotic at birth, and a loud systolic murmur was heard at that time. Squatting, dyspnea on exertion, and increasing cyanosis appeared after the patient began to walk. At the time of admission, he could walk only two blocks and could climb one flight of stairs with great difficulty. There was no history of epistaxis, hemoptysis, spells, or congestive cardiac failure.

On physical examination, the patient was well developed and nourished and showed moderate cyanosis and clubbing. Temperature was 99.2 F., pulse rate 100, respirations 20 per minute, and blood pressure 110/80 (left arm). There was no peripheral edema, distention of neck veins, or chest deformity. Femoral and radial pulses were equal and strong. The liver extended 3 cm. below the right costal margin in the nipple line. The apex was in the fifth left intercostal space, 1.5 cm. beyond the midclavicular line. No thrills were present. The first sound was normal, but the second sound was very loud and single in the region of the third left intercostal space near the sternum. *There was a rough, grade IV, systolic murmur which was loudest in the*



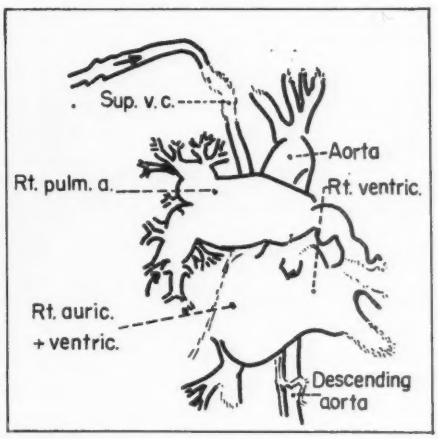


FIG. 4*a*. Chest film of case 2. Note the engorged vascular pattern on the right.

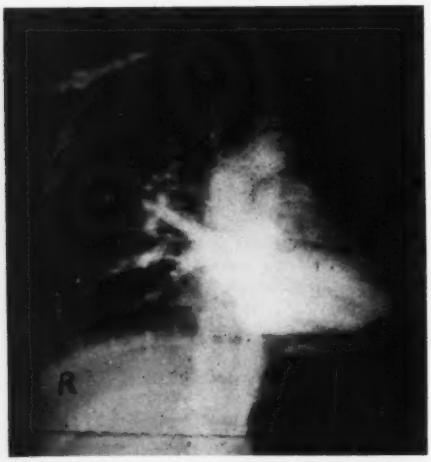
while the right ventricular pressure was 72/5. This pressure change occurred abruptly at the pulmonic valve, suggesting a valvular stenosis. Repeated attempts to enter the left pulmonary artery were unsuccessful. Analysis of blood samples obtained revealed an oxygen saturation in the femoral artery

second and third right intercostal spaces near the sternum (fig. 5). This murmur was transmitted to the entire right chest and to the precordium.

The hemoglobin was 21.0 Gm., the erythrocyte count 8.0 million, and the hematocrit 69 per cent. Circulation time, arm to tongue (fluorescein), was 8

seconds. The electrocardiogram showed right axis deviation, atrial hypertrophy, and marked right ventricular hypertrophy.

definite prominence of the right ventricle. Normal pulmonary artery pulsations were absent along the upper left cardiac border; however, no concavity was



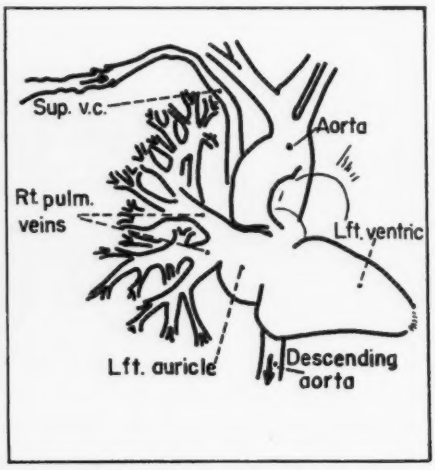


FIG. 4*b*. Angiocardiogram of case 2. Note large right main and absent left main pulmonary artery.

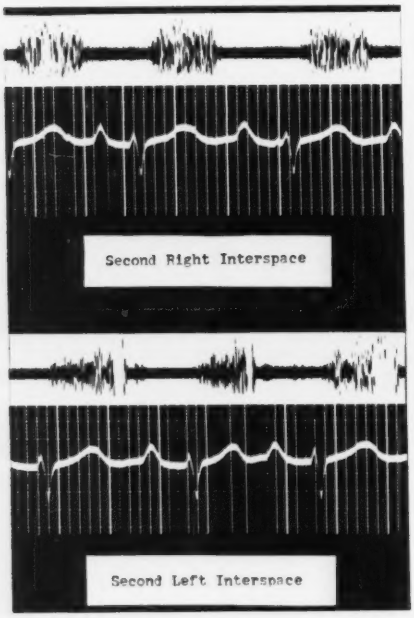


FIG. 5. Phonocardiogram of case 3. Note the diamond-shaped systolic murmur which is more intense on the right than on the left.

Films and fluoroscopic examination of the chest showed the heart to be slightly enlarged with

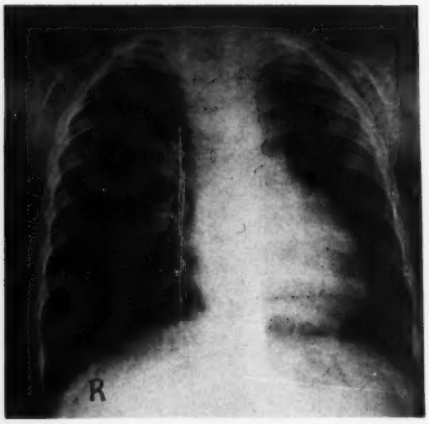


FIG. 6. Chest film of case 3.

seen in this area. *The branches of the right pulmonary artery were markedly engorged, whereas the vascular markings in the left lung were strikingly diminished* (fig. 6). The aortic arch was on the left.

An angiocardiogram showed simultaneous filling of a dilated right pulmonary artery and the aorta (fig. 7). The left pulmonary artery and its branches were not visualized, indicating absence, atresia, or marked stenosis of this vessel. Later films showed the aorta being refilled from the left ventricle.

A cardiac catheter was passed through the right atrium and right ventricle into the aorta. Despite

repeated efforts, it was impossible to pass the catheter into the pulmonary artery. Right ventricular pressure was 85/5. The oxygen saturation in the femoral artery was 70 per cent, and there was a right-to-left shunt of 6.4 liters per square meter of body surface area per minute.

Films and fluoroscopic examination of the chest confirmed the clinical and electrocardiographic impressions of dextrocardia and situs inversus. There was slight cardiac enlargement with prominence of the transposed right ventricle. *The right pulmonary vascular markings were markedly decreased in number*

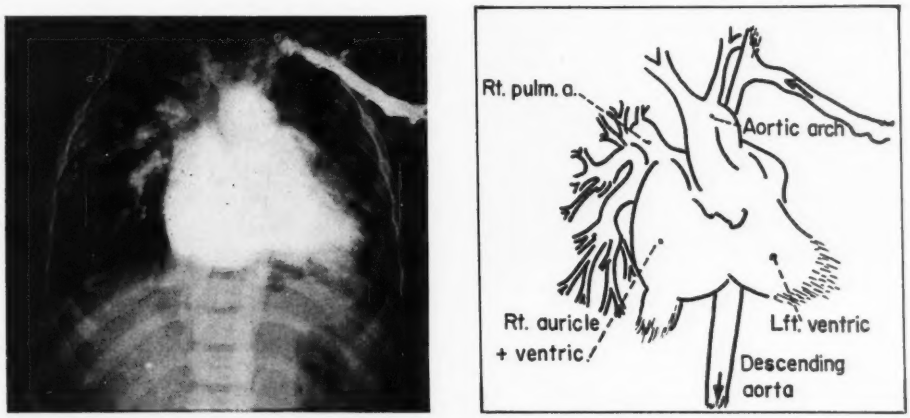


FIG. 7. Angiocardiogram of case 3.

Case 4. L. A. LaF. (no. 391487). This 3 11/12 year old white girl had been cyanotic since birth. Occasional squatting and mild dyspnea on exertion appeared at 1½ years of age but had not increased since that time. There was no history of epistaxis, hemoptysis, or congestive cardiac failure.

Physical examination revealed a well developed and well nourished little girl in no acute distress. Temperature was 99.0 F., pulse rate 120, respirations 18 per minute, and blood pressure 95/78 (left arm). There was evidence of spinal anomalies with shortening and atrophy of the right lower extremity. Marked cyanosis and clubbing and moderate right-sided chest deformity were present. Femoral pulsations were strong. There was no peripheral edema, distention of neck veins, or hepatomegaly. The apex was in the fifth right intercostal space, 1.0 cm. beyond the right midclavicular line. The first sound was loud at the lower right sternal border, and the second sound was definitely diminished at the base. There was a grade III, rough systolic murmur, loudest between the lower right sternal border and the apex. *Another systolic murmur, grade IV in intensity,* was best heard at the second left intercostal space near the sternum.

The hemoglobin was 21.5 Gm., the erythrocyte count 7.0 million, and the hematocrit 71 per cent. The circulation time, arm to tongue (fluorescein), was 7.5 seconds. The electrocardiogram showed dextrocardia with probable right ventricular hypertrophy.

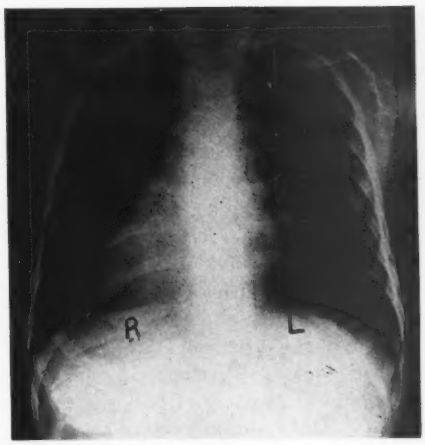


FIG. 8. Chest film of case 4. Note the increased vasculature in the left chest.

and caliber, while the vascular markings on the left were prominent and abundant (fig. 8). There was a right aortic arch with a right descending aorta.

An angiocardiogram showed simultaneous early filling of the aorta and the left pulmonary artery (fig. 9). No contrast medium was seen in the right lung until much later when a very small amount appeared, apparently reaching the right lung from a small branch of the aorta.

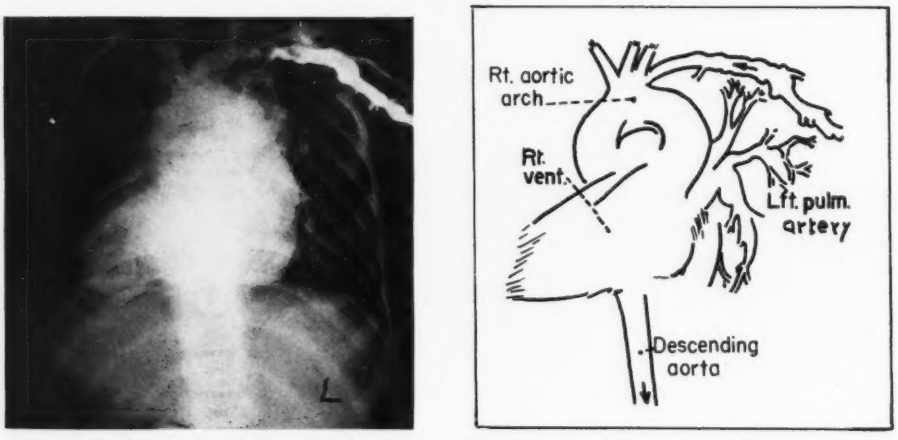


FIG. 9. Angiocardiogram of case 4. Note early filling of aorta and left main pulmonary artery.

DISCUSSION

The tetralogy of Fallot syndrome consists of pulmonic stenosis, right ventricular hypertrophy, ventricular septal defect, and dextroposition of the aorta. The pulmonic stenosis encountered in this condition may be subvalvular or valvular in location. The pulmonary artery and its left and right main branches show varying degrees of hypoplasia, which is classically symmetric and probably roughly proportionate to the stenosis of the outflow tract. The present group of patients can be set apart from the usual picture of the tetralogy of Fallot cases by the fact that, in addition to the stenosis of the valvular or subvalvular area, they all showed atresia (functional or anatomic) of one main pulmonary artery with dilatation of the other.

The only detailed pathologic report in the literature of a tetralogy of Fallot patient with absence of one main pulmonary artery is that of Thomas[5] in 1941. Blalock[6] states that out of 610 patients with cyanotic congenital heart disease, he has encountered nine cases with absence of one pulmonary artery. He does not state the relative frequency with which each of the two sides was involved, but the two patients he has used as illustrations in this and another publication[7] show the left main pulmonary artery to be absent.

It seems more than coincidental that all three of these documented cases and all three of our patients with the heart in normal position showed atresia of the *left* main pulmonary artery with dilatation of the *right* main vessel, especially since our one case with dextrocardia is the only one to our knowledge in which atresia of the *right* pulmonary artery is accompanied by dilatation of the *left*.

This correlation of atresia of the *left* main pulmonary artery with the tetralogy of Fallot syndrome becomes even more interesting when we consider the fact that all the reported instances of atresia of one pulmonary artery without intrinsic heart disease affected the *right* pulmonary artery.[8–14] We have one such patient under observation at present at the Children's Medical Center in Boston.

To the best of our knowledge, no clinical criteria have so far been outlined to differentiate the present group of patients from the conventional type of tetralogy of Fallot cases. We believe, on the basis of the findings in our four patients, that such a differential diagnosis is possible on the following grounds:

(a) *The systolic murmur* of tetralogy of Fallot, if present, is always best heard at the left sternal border and transmits best to the left chest and the left clavicle. Our three patients with the heart in normal position demonstrated systolic murmurs with maximal intensity in the right chest and under the right clavicle.

Patients with tetralogy of Fallot and dex-

trocardia usually demonstrate systolic murmurs best audible over the right chest and under the right clavicle, whereas our one patient with dextrocardia had a murmur much louder under the left clavicle.

These auscultatory phenomena may well be due to the propagation of the murmur in the direction of the pulmonary blood flow.

(b) *The roentgenologic examination* of patients with tetralogy of Fallot almost invariably shows a symmetric diminution of the pulmonary vascular pattern in the lung fields. In the cases with tetralogy of Fallot and unilateral pulmonary atresia, the affected side shows marked diminution of the pulmonary vasculature, whereas the side with the dilated main pulmonary artery demonstrated evidences of pulmonary vascular engorgement, occasionally even with a "hilar dance."

(c) *Angiocardiographic* studies confirm the presence of this entity by demonstrating an overriding aorta, atresia of one main pulmonary artery, and aneurysmal dilatation of the other.

(d) *Cardiac catheterization* studies demonstrate the presence of pulmonary stenosis. It is interesting to note that in two of our patients, catheterization strongly suggested the presence of a valvular stenosis—a finding also present in our one autopsied case.

Discussing the operative hazards in patients with a single pulmonary artery, Blalock[6] makes the statement that the risk is much higher in these cases than in patients with the conventional tetralogy of Fallot. The danger occurs at the time in the procedure when it is necessary to occlude completely the only pulmonary artery available, thereby stopping the entire pulmonary circulation, save for the blood reaching the lungs through collaterals. The danger inherent in this set of circumstances was well demonstrated during the operation on case 1 when momentary compression of the right pulmonary artery resulted in a rapid and significant drop in arterial oxygen saturation.

Although a shunt procedure may have to be attempted in a severe case of tetralogy of Fallot with unilateral pulmonary atresia, the indications for operation should clearly be much more stringent than under ordinary circumstances.

One may speculate on the feasibility of attempting a Brock procedure in these patients, but the autopsy findings of absent semilunar cusps in our patient and in Thomas' case make one hesitate to make such a recommendation, except as a last resort.

Summary

1. Three patients with tetralogy of Fallot and atresia of the left main pulmonary artery are reported. All three have shown an associated dilatation of the right main pulmonary artery with pulmonary vascular engorgement on this side.

2. One patient with dextrocardia and tetralogy of Fallot showed atresia of the right main pulmonary artery with dilatation of the left.

3. Clinical and radiologic points in the differential diagnosis of these conditions are stressed.

4. The increased operative hazards represented by these patients are discussed.

Sumario Español

Se presentan en este informe cuatro pacientes con el síndrome de la tetralogía de Fallot, cuyos hallazgos físicos y radiológicos fueron distintamente poco usuales. En todos estos pacientes se demostró una atresia funcional o anatómica de una de las arterias pulmonares en adición a los hallazgos característicos de la tetralogía de Fallot. Criterio diagnóstico, incluyendo angiocardiogramas, se presentan; y las inferencias terapeúticas se discuten.

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Rheumatic "Activity" as Judged by the Presence of Aschoff Bodies in Auricular Appendages of Patients with Mitral Stenosis

II. Clinical Aspects

By WILLIAM F. MCNEELY, M.D., LAURENCE B. ELLIS, M.D., AND DWIGHT E. HARKEN, M.D.

Clinical data have been correlated with heart muscle biopsy findings in 183 patients undergoing operation for mitral stenosis. It was not possible to relate the finding of Aschoff lesions to the usual clinical or laboratory evidences of rheumatic carditis, although older patients and those exhibiting auricular fibrillation were least likely to be histologically "active." The possible significance of these findings is discussed.

THE SURGICAL treatment of mitral stenosis has provided, for the first time, biopsy material from the hearts of a large number of living rheumatic individuals. Histologic finding of Aschoff lesions in these specimens was mentioned in an article from this laboratory in 1951.[1] Since that time other reports have described the pathologic findings and have attempted, in some instances, to relate the "positive" biopsy to certain features of the patients' illness.[2-5]

This opportunity to correlate pathologic findings in vivo with the clinical state of the patient is important. It may lead to information regarding the vexing questions of subclinical rheumatic activity in patients with chronic rheumatic heart disease, and the significance of the Aschoff body as representing rheumatic activity. Furthermore, it is important to determine whether the presence of these Aschoff lesions influences the operative and postoperative course of patients, in relation to mortality or other complications. The present study is concerned with a correlation of clinical features with histologic findings. The details of the morphologic changes are reported separately.[6]

Presented before the New England Cardiovascular Society, Boston, Nov. 17, 1952.

From the Thorndike Memorial Laboratory and the Second and Fourth Medical Services (Harvard), Boston City Hospital, and the Departments of Medicine and Surgery, Harvard Medical School.

This study was supported in part by a grant from the National Heart Institute.

METHODS

All biopsies of the left auricular appendage taken at the time of mitral valve surgery between Dec. 2, 1949 and July 1, 1952 were reviewed by the pathologists, Drs. J. P. Decker, C. Van Z. Hawn and S. L. Robbins. This material was classified according to the presence and number of Aschoff lesions, with a notation as to presence or absence of intra-auricular thrombus. Of this consecutive series of 223 biopsies, 17 were excluded because of inadequate size of the specimen or for other technical reasons. It was also necessary to exclude 23 more patients because their clinical records were unsatisfactory or not readily available. The remaining 183 records were tabulated and the findings entered on punch cards. It is understood that unless otherwise specified, positive biopsy refers to the finding of Aschoff lesions in any degree, whether graded 1, 2, or 3 plus.

RESULTS (TABLES 1 AND 2)

The detailed pathologic findings have been reported in another communication.[6] From that study it was found that 45.4 per cent of left auricular biopsy specimens contained Aschoff lesions indistinguishable from those found in hearts of patients dying with clinical rheumatic fever. This was despite the fact that at that time patients with clinically obvious active rheumatic fever were not sent to

TABLE 1.—*Historical Details, Physical Findings, and Laboratory Data Tabulated According to Auricular Biopsy Diagnosis*

		No. Patients					No. Patients		
		"Positive"		Neg.			"Positive"		Neg.
		1+	2-3+				1+	2-3+	
Hospital	BCH*	3	15	23	History of rheumatic fever	None	10	20	47
	PBBH†	25	40	77		Present	18	35	53
Age	20-30	7	18	9	History of S.B.E.‡	None	26	50	94
	31-40	14	30	37		Present	2	5	6
	41-50	7	6	42	Sodium restriction	None	10	11	14
	51-62	0	1	12		Present	11	29	66
Sex	Female	20	43	60	Digitalis	None	6	4	3
	Male	8	12	40		Yes	21	50	96
Group	II	1	2	2	Ammonium chloride	None	13	23	34
	III	22	45	56		Yes	6	21	36
	IV	5	8	42	Mercurial	None	12	18	26
Month	Jan.	1	2	8		Less than 1/week	7	17	33
	Feb.	1	6	9		1/week or more	3	14	26
	March	4	6	7	Suspicious activity	None	27	47	92
	April	4	6	10		Yes	1	8	8
	May	1	5	21	X-ray enlargement	None	4	18	7
	June	2	7	13		Sl.-Mod.	13	27	47
	July	4	4	4		Marked	8	4	36
	Aug.	0	0	4	X-ray—Mitral calcification	None	14	33	51
	Sept.	2	5	4		Yes	8	10	32
	Oct.	4	5	11	Apical systolic murmur	None	12	32	36
	Nov.	0	4	2		Gr. 1-2	12	14	45
	Dec.	4	5	7		Gr. 3+	4	8	19
Dyspnea	None	0	0	0	Apical diastolic murmur	None	1	0	0
	Sl.-Mod.	13	32	57		Gr. 1-2	9	12	43
	Marked	14	23	43		Gr. 3+	18	43	57
Pulmonary edema	None	9	19	38	Aortic and/or pulmonary diastolic murmur	None	16	31	60
	Sl.-Mod.	9	19	28		Yes	12	24	40
	Marked	2	4	5					
Orthopnea	None	6	21	24	Tricuspid murmur	None	23	45	80
	Sl.-Mod.	17	27	59		Yes	5	7	15
	Marked	3	6	12	Pulmonary systolic murmur	None	24	46	90
Paroxysmal dyspnea	None	7	25	34		Yes	4	9	10
	Sl.-Mod.	17	27	49	Blood pressure above 145/90	No	26	50	84
	Marked	1	1	7		Yes	1	1	10
Hemoptysis	None	11	17	47	ECG rhythm	N.S.R.§	18	47	21
	Sl.-Mod.	12	33	43		A.F.‖	9	7	79
	Marked	4	2	1	ECG auricular enlargement (all N.S.R.)	None	8	13	3
Chest pain	None	11	22	40		Yes	10	34	18
	Sl.-Mod.	15	25	42					
	Marked	1	3	3	ECG, right ventricular hypertrophy	None	13	32	52
Edema	None	13	24	39		Yes	14	19	46
	Sl.-Mod.	15	29	55	ECG, left ventricular hypertrophy	None	22	49	84
	Marked	0	2	6		Yes	4	2	13
Enlarged liver	None	12	26	25	P-R prolongation	None	15	42	15
	Sl.-Mod.	10	20	30		1st deg.	3	4	6
	Marked	6	9	44		2nd deg.	0	1	0
Fatigue	None	22	7	9	Right bundle branch block	None	24	46	85
	Sl.-Mod.	11	25	55		Incompl.	1	8	14
	Marked	11	10	19		Compl.	2	0	1
Emboli	None	24	45	67	Q-T interval	Norm.	2	11	13
	Present	4	10	33		Prol.	1	3	7

TABLE. 1—*Continued*

		No. Patients					No. Patients		
		"Positive"		Neg.			"Positive"		Neg.
		1+	2-3+				1+	2-3+	
Venous pressure	Norm.	15	33	40	Surg. thromb.	No	9	20	21
	Incr.	9	9	42		Yes	3	2	42
Sed. rate	Norm.	13	26	43	Surg. regurg.	No	12	28	32
	Incr.	13	22	43		Yes	11	17	44
(No hepato-megaly)					Operative or Postoperative Complications				
Sed. rate	Norm.	6	15	10	Shock	No	23	49	78
	Incr.	5	8	9		Yes	5	6	22
Circ. time	Norm.	7	19	5	Arrhythmia	No	17	42	81
	Incr.	17	29	77		Yes	11	13	19
Surg. type[9]	I.	6	26	38	Embolus	No	20	45	84
	II.	3	12	15		Yes	8	10	16
Surg. group[9]	A.	6	29	30	Pulmonary edema	No	27	54	97
	B.	3	6	20		Yes	1	1	3
Surg. calcif.	No	8	27	26	Cardiac arrest	No	28	51	91
	Yes	7	15	31		Yes	0	4	9
					Death	No	26	50	81
						Yes	2	5	19

* Boston City Hospital.
† Peter Bent Brigham Hospital.
‡ Subacute bacterial endocarditis.
§ Normal sinus rhythm.
‖ Auricular fibrillation.

surgery. Furthermore, a comparison of these biopsy findings with more conventional autopsy sections of the heart in 21 patients who died, showed sufficiently close correlation to validate the left auricular appendage as an adequate site for histologic evaluation of Aschoff bodies.

Forty-one of these patients were operated at the Boston City Hospital and 142 at the Peter Bent Brigham Hospital. The percentage of positive biopsies was similar (Boston City Hospital 43.9 per cent and Peter Bent Brigham Hospital 45.8 per cent).

An arrangement of patients according to age group showed a progressive decline in percentage of positive biopsies with advancing age (fig. 1). Thus 73 per cent of patients aged 20 to 30 showed Aschoff lesions as against only 8 per cent of those past 50. For purposes of analysis, the patients have been divided into two groups, 104 "young" patients aged 20 to 39, and 77 "old" patients 40 years and above. The difference in percentage of positive biopsies between the two groups is highly significant.

There were 123 females and 60 males, a ratio of approximately 2:1. Of the females, 51.2 per cent had positive biopsies, as against 33.3 per cent for the males. The difference is barely significant, yet the figures are remarkably consistent for the two hospital groups: 50 per cent and 35 per cent for Boston City Hospital, 51.5 per cent and 32.5 per cent for Peter Bent Brigham Hospital. It is not possible to attribute this difference entirely to age (females 37.6 years mean, males 39.2 years mean), or to rhythm (females 50 per cent and males 42 per cent normal sinus rhythm).

Tabulation of histologic findings against date of operation disclosed no obvious seasonal variation in prevalence of the Aschoff lesion. It would appear unlikely, then, that these lesions were associated necessarily with recent streptococcal infection prior to surgery.

After the patients' age, the second major factor concerned with the presence of Aschoff bodies was found to be the heart rhythm. Of 86 patients in normal sinus rhythm, 65 showed Aschoff lesions, or 76 per cent. Of 95 with auricular fibrillation, there were only 16, or 17 per cent, with Aschoff lesions. As is apparent in figure 1, the difference was true for all age groups of any adequate size, although the

TABLE 2.—*Statistical Calculations*

	No Hepatomegaly	Hepatomegaly	Chi²		Normal C.T.	Incr. C.T.	Chi²
Pos.	38	43	8.26	Pos.	25	45	19.1
Neg. (N.S.R.)	25	74		Neg. (N.S.R.)	5	77	
Pos.	33	32	<1.0	Pos.	24	33	4.1
Neg. (A.F.)	11	10		Neg. (A.F.)	3	18	
Pos.	5	11	<1.0	Pos.	1	12	<1.0
Neg.	14	64		Neg.	2	59	
	No Cardiomegaly	**Cardiomegaly**	**Chi²**		**Normal V.P.**	**Incr. V.P.**	**Chi²**
Pos.	21	51	11.3	Pos.	46	18	6.9
Neg. (N.S.R.)	7	83		Neg. (N.S.R.)	40	42	
Pos.	21	38	<1.0	Pos.	39	12	1.2
Neg. (A.F.)	4	15		Neg. (A.F.)	12	8	
Pos.	0	13	<1.0	Pos.	7	6	<1.0
Neg.	3	68		Neg.	28	34	
	Group III	**Group IV**	**Chi²**		**No Emboli**	**Emboli**	**Chi²**
Pos.	67	13	13.4	Pos.	67	14	4.96
Neg. (N.S.R.)	56	42		Neg. (N.S.R.)	67	33	
Pos.	56	6	<1.0	Pos.	56	9	<1.0
Neg. (A.F.)	16	4		Neg. (A.F.)	16	5	
Pos.	9	7	<1.0	Pos.	11	5	<1.0
Neg.	40	38		Neg.	51	28	

	N.S.R.	A.F.	Chi²
Pos.	65	16	60.
Neg. ("Young")	21	79	
Pos.	53	10	22.9
Neg. ("Old")	15	26	
Pos.	12	6	21.5
Neg.	6	53	

Pos.: Positive Biopsy
Neg.: Negative Biopsy
N.S.R.: Normal Sinus Rhythm
A.F.: Auricular Fibrillation
C.T.: Circulation Time
V.P.: Venous Pressure

progressive decrease with advancing age remains evident throughout. In an attempt to evaluate the effect of fibrillation independent of age, four-fold contingency tables have been set up for rhythm vs. biopsy diagnosis for both "young" and "old" groups of patients. The association is highly significant for both groups, and is compatible with some inverse relationship with auricular fibrillation apart from chronologic age of the patient.*

Individuals showing any of the following

* Two patients are excluded from the grand total of 183 because of missing electrocardiograms. However, both of these were females with positive biopsies, both with clinically regular rhythm and presystolic accentuation of the mitral diastolic murmur.

factors were found to have a significantly lower percentage of positive biopsies: a history of pulmonary or peripheral embolus, palpable enlargement of the liver, venous pressure greater than 120 mm. saline, prolonged circulation time (Decholin 16 seconds, magnesium sulfate 19 seconds), or radiologic evidence of cardiac enlargement. However, a breakdown of all of the items according to heart rhythm shows that the lower incidence holds only for patients in each category who were fibrillating, whereas those in normal sinus rhythm had no difference in percentage of positive biopsies from the series as a whole. It is to be emphasized that measurement of heart size by radiologic methods represented in each instance a single observation, and did not take into account *changes* in heart size over a period of time.[7, 13]

It is conceivable that the relationship between fibrillation and biopsy might be due solely to duration of the rheumatic process, for example, that a young person with auricular fibrillation has had his disease longer than a patient of comparable age in normal sinus rhythm. In 46 patients some estimate of duration of auricular fibrillation was available. Eight of these patients had positive biopsies; of these, three had been fibrillating one year or less, one had been fibrillating two years, one four years, one nine years, and two 20 years or longer. Among 106 patients able to remember and date an attack of rheumatic fever, there occurred a similar lack of clear relationship between time since last known rheumatic attack and the presence of Aschoff lesions.

Apart from the significance of rhythm, the electrocardiogram did not provide a clue to "activity." Prolongation of the P-R interval was found in 14 instances; of these, eight had positive biopsies (57.1 per cent), a relationship not appreciably different from the group as a whole. Some of these instances of partial auriculoventricular block may have been related to digitalis since all but one of these 14 patients were digitalized; however, the one undigitalized patient had a negative biopsy despite a P-R interval of 0.24 second.

The Q-T interval was measured and corrected by a modification of the Taran technic[8] in 39 patients of the Boston City Hospital group, with a finding of no significant difference in Bazett's K between the positive and negative groups (mean K was 0.370 and 0.368 second respectively). Thirty-five of the 39 patients were digitalized, so that some abnormal prolongation might conceivably have been disguised by digitalis. Also, K was never greatly prolonged, in no instance exceeding 0.435 second.

Erythrocyte sedimentation rate (Wintrobe) was performed routinely. It was not found to be of value, whether normal or markedly elevated. This is at variance with a recent report by Sabiston and Follis.[5] Since hepatic congestion might be expected to alter plasma protein relationships and hence the sedimentation rate, a regrouping of patients was made, excluding those showing any palpable degree of liver enlargement. It was still impossible to show any relationship between sedimentation rate and biopsy.

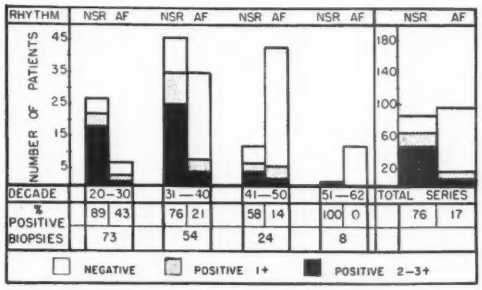

FIG. 1. Auricular biopsies by rhythm and decade.

Not included in the present series are a number of antistreptolysin-0 titers* performed routinely in 43 consecutive cases. There was no significant association between biopsy finding and antistreptolysin titer, in contrast to the report of Biörck and co-workers.[4] The routinely rather low level of antistreptolysin-0 titer is probably further evidence against recent streptococcal infections in this group of patients.

Leukocyte counts and temperature during preoperative hospitalization were not tabulated as they were generally normal, and when ab-

* Antistreptolysin determinations were performed at the House of the Good Samaritan through the courtesy of Dr. Benedict F. Massell.

normal could often be explained by respiratory infection or other obvious cause.

On many occasions the surgeon recorded an opinion as to the presence of grossly palpable clot within the auricle at the time of cardiotomy. As might be expected because of the association with fibrillation, presence of a surgically evident thrombus reduced the likelihood of a positive biopsy considerably. The presence of histologic clot within the biopsy specimen was found to have a similar association.[6] There were too few instances of thrombus in the presence of normal sinus rhythm to permit an evaluation of the effect of thrombus independent of auricular fibrillation.

There was no significant difference in biopsy findings in patients with a preoperative diagnosis of pure mitral stenosis as contrasted with those thought to have some degree of mitral regurgitation or lesion of other valves. Similarly there was no difference when compared according to anatomic diagnosis established at operation.

For purposes of estimating surgical prognosis, all patients were classified preoperatively into one of four classes according to the criteria of Harken and his associates.[9] Group IV, the "terminal" group, had a significantly lower percentage of positive biopsies than had group III (23.6 per cent and 54.1 per cent, respectively). As previously stated, it can be shown that this difference holds only for the older patients with auricular fibrillation of group IV. There were three positive out of five biopsies in group II, but the number is too small to be of significance. No group I patients have been operated.

The final observation of major importance from the standpoint of surgical treatment of these patients is the incidence of operative and postoperative complications according to biopsy. As can be seen from the table, there is no higher incidence of operative complications or mortality in the positive group.

Comment

For many years it has been appreciated that a significant proportion of rheumatic hearts at autopsy examination show clinically unsuspected evidences of rheumatic "activity" as manifested by Aschoff lesions.[10-12] Furthermore, it is evident from autopsy series in which age is included that the frequency of occurrence of the Aschoff lesion decreases with advancing age much as in the present series. Thus, from the autopsy series reported by Rothschild and co-workers,[10] the percentages of hearts showing Aschoff lesions were: third decade 69 per cent, fourth decade 70 per cent, fifth decade 38 per cent and sixth decade 13 per cent. Figures by comparable decade for the present biopsy series are 71 per cent, 54 per cent, 24 per cent, and 8 per cent. In addition, Bland and Jones[13] reported a similar decrease in frequency of recurrence of clinical rheumatic fever with passage of time since the initial attack.

Our studies have demonstrated a lower incidence of positive biopsies in patients with auricular fibrillation. Fibrillation correlates well with the presence of intra-auricular thrombus, and from the available data, there is no way of evaluating the effect of fibrillation or thrombus independently of one another. However, it has been stated in the past[14, 15] that thrombus within the auricle is uncommonly found in hearts showing Aschoff lesions, so that an inverse relationship with auricular fibrillation might have been suspected. Such autopsy reports as are available do not provide sufficient clinical data for a direct correlation between rhythm and thrombus formation.

Although none of these findings is unique, it is still noteworthy that these instances of unsuspected "activity" occurred in a series of patients in which careful elimination of clinically active individuals was carried out; this was not done in the reported autopsy series. The difficulty of clinical evaluation of activity is illustrated by the following observation: although no patient was operated at a time when definite rheumatic fever was evident, there were several instances in which one or more experienced observers were exceedingly suspicious of active rheumatic carditis at some time during the preoperative hospital course. The over-all incidence of nine positive biopsies in this small group of 17 patients (52.9 per cent) is essentially the same as for the total series. It is of interest that in three cases, full courses of corticotropin (ACTH) or cortisone

had been administered during preoperative hospitalization for presumed active carditis. Biopsy in these three cases was negative, and was positive in a fourth patient who had received an unknown amount of cortisone six months earlier.

As has been seen, the biopsy finding can be predicted with fair statistical accuracy only when the age of the patient falls toward one or the other extreme, and then only when related to the cardiac rhythm. It is evident that other clinical data (including some of the more popular tests for rheumatic fever) are not useful in this regard. In addition, the Aschoff lesion is not associated with any increase in operative mortality or morbidity in contrast to what might be expected in the case of clinically active rheumatic fever. For practical purposes, it would appear that histologically active patients do as well as the rest, if not better. For this reason, in the absence of definite clinical evidence of activity, positive biopsy alone has not been considered adequate cause to alter in any way the routine postoperative management of these patients. Whether such an attitude is indeed correct will depend upon the result of long-term follow-up studies that are being carried on. There are, however, no findings in the present study which would justify surgical treatment in patients with clinically obvious rheumatic carditis.

The most difficult task of all is to attempt to explain the significance of these biopsy findings in relation to clinical rheumatic fever. There is nothing in the present communication either to prove or disprove a relationship between Aschoff lesions and a continuing active rheumatic state. If this state truly represents "smoldering" rheumatic carditis, then the currently available clinical technics are not specific enough to demonstrate it. Further light on this problem might be shed by similar studies of hearts afflicted with other forms of rheumatic valvular disease.

The present report does not justify any conclusions concerning the clinical diagnosis of rheumatic carditis and its relation to use of adrenal steroid therapy.

Summary

The records of 183 patients operated upon for mitral stenosis have been reviewed. Biopsy of the left auricular appendage was provided by this operation. Forty-five per cent of these biopsies contained Aschoff lesions, although all patients with clinically obvious active rheumatic fever had been eliminated prior to surgery.

Review of the clinical records of these patients failed to show any definite correlation between Aschoff bodies and the usual clinical or laboratory criteria of rheumatic activity (for example, high sedimentation rate, elevated antistreptolysin-0 titer, and prolonged P-R or Q-T interval). There was, however, a progressive decline in percentage of positive biopsies with advancing age. In addition, there was a lower percentage of positive biopsies in patients with auricular fibrillation in all age groups, as well as in those hearts showing histologic evidence of auricular thrombus. The Aschoff lesions did not show seasonal variation. The significance of these findings with respect to the management of these patients and to clinical rheumatic fever is discussed.

Sumario Español

Los datos clínicos han sido correlacionados a los hallazgos de biopsia del músculo cardíaco en 183 pacientes que fueron sometidos a la operación para estenosis mitral. No fué posible relacionar los hallazgos de lesiones de Aschoff a la evidencia usual clínica y de laboratorio de carditis reumática, aunque pacientes mayores y aquellos que sufrían con fibrilación auricular fueron los menos probables de mostrar actividad histológica. El posible significado de estos hallazgos se discute.

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Hemodynamic Effects of Valvulotomy in Pulmonic Stenosis

By PAUL R. LURIE, M.D., AND HARRIS B. SHUMACKER, JR., M.D.

Seven patients with mild to moderate pulmonic stenosis with intact ventricular septum were subjected to cardiac catheterization before and from 4 to 18 months after pulmonary valvulotomy. Despite uniform clinical improvement, remarkably slight changes were observed, following surgery, in right ventricular pressure, pulmonary artery pressure, pulmonary artery flow, and pulmonary valve area, when measured at rest. When present preoperatively, venoarterial shunt was reduced or eliminated after operation. It was speculated that further studies including the effect of exercise might show that valvulotomy increases the mobility of the valve under stress even when it does not increase valve area at rest.

WHENEVER the diagnosis of pulmonic stenosis with intact ventricular septum is established, the question of the advisability of pulmonary valvulotomy arises. There is at present little doubt of the propriety of operative intervention in those patients manifesting marked cyanosis, or severe dyspnea and fatigue on slight exertion, or evidence of congestive heart failure. No such unanimity exists as to the indications for surgery in milder cases.[1-4] A more complete understanding of the hemodynamic effects of the Brock type valvulotomy[5] as practiced at present would contribute toward a sounder formulation of criteria for operability, and toward an evaluation of the effectiveness of the operation itself.

Physiologic studies comparing the preoperative and postoperative status of such patients are few. The postoperative findings in three cases of the present group have been briefly mentioned elsewhere.[6] Galligan and colleagues[3] have published postoperative right ventricular pressures in two cases. Right ventricular and pulmonary artery pressures with the chest open before and after valvulotomy have also been mentioned[1, 6, 7] and used by one group as a guide in the decision to open the valve further at that operation.[7] A pressure curve taken at operation by Brock in one published case shows a very satisfactory immediate response with lowering of right ventricular systolic pressure from about 80 to about 40 mm. Hg, and a slight increase in pulmonary artery pressure. However, others[4, 8] have alluded to unpublished data expressing concern about the fact that right ventricular pressure has remained elevated after surgery.

CASE MATERIAL

Seven patients who had had a cardiac catheterization and other physiologic studies before surgery were subjected to a postoperative catheterization. The interval between surgery and catheterization ranged from 4 to 18 months. While none of these patients had any of the unquestionable qualifications for surgery mentioned above, they all had symptoms of mild to moderate degree.* All enthusiastically cited evidences of increased exercise tolerance after surgery.

METHODS

The catheterizations were performed in a "basal state" in accordance with accepted methods.[9, 10, 11] Pressures were measured with a Hathaway impedance gauge. Mean pressures were found by planimetric integration. The catheters were 6F or 7F, with birdseye tips. The oxygen utilization was

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* The clinical status of these patients has been adequately discussed elsewhere.[6] To avoid confusion, the same patient numbers are used in reporting the present results. Since patient 4 in the previous report was not catheterized, there is no patient 4 in the present paper. Since the previous report, all patients have continued to experience the same or even greater improvement. Patient 7 went through pregnancy and labor uneventfully.

measured by the analysis of the contents of a timed Douglas bag sample of expired air in all but the preoperative studies of the first three patients which were performed before gas analysis facilities were available. In these patients those preoperative values which are prefixed in the tables by a question mark have been estimated by assuming an oxygen consumption identical with that measured in the postoperative study. Arterial oxygen saturation studies were performed and evaluated according to methods and standards described fully elsewhere.[11] Briefly stated, venoarterial shunt was indicated by failure of arterial blood to become fully saturated during the five minute inhalation of pure oxygen. "Lung factor" was calculated according to the formula of Ordway,[12] from the rise in oxygen content of arterial blood produced by the inhalation of pure oxygen. This factor represents the fraction of total hemoglobin which passes through aerated lung without becoming oxygenated when the patient breathes room air. The method of Gorlin and Gorlin[13] was used to compute pulmonary valve area, using their suggested constant for both preoperative and postoperative catheterizations.

Results

Arterial Oxygen Saturation. These studies are presented in table 1. Venoarterial shunt, when found in association with pulmonic stenosis and intact ventricular septum, is thought to be via either a functionally patent foramen ovale or an atrial septal defect. Four of these patients had definite venoarterial shunt before surgery. Evidence of shunt disappeared completely in two and was reduced to borderline degree in two. In another case, venoarterial shunt which was intermittent before surgery was not evident after operation, but postoperatively lung factor increased to an abnormal degree. A borderline venoarterial shunt was unaltered by surgery in one case. Another patient who before surgery had abnormal lung factor but no venoarterial shunt was unchanged postoperatively.

Pressures. These data are presented in table 2. The right ventricular pressures, elevated to

Table 1.—*Arterial Oxygen Saturation Studies in Cases of Pulmonic Stenosis with Intact Ventricular Septum, before and after Pulmonary Valvulotomy*

Case No.	Time of Test	Arterial Oxygen Saturation, %		Classification
		Breathing Room Air	Breathing Pure Oxygen Possible Range and Mean	
1	Before	89.0	89.2—90.9—92.6	Definite venoarterial shunt
	18.5 mos. after	91.8	95.1—97.1—99.2	Borderline, possible small venoarterial shunt
2	Before	91.2	95.9—98.1—100.3	Borderline, possible small venoarterial shunt
	8.5 mos. after	92.2	97.2—99.3—101.4	Borderline, possible small venoarterial shunt
3	Before	91.4	94.4—96.5—98.6	Definite venoarterial shunt
	7.5 mos. after	94.9	102.4—104.6—106.8	Normal
5	Before	91.3	94.6—96.6—98.7	Definite venoarterial shunt
	Before (on another day)	89.3–96.8		Intermittent shunt
	12 mos. after	90.8	99.0—101.1—103.3	Definite lung factor, probably no venoarterial shunt
6	Before	87.7	86.3—88.5—90.6	Definite venoarterial shunt
	6.5 mos. after	94.3	98.1—100.5—102.9	Borderline, possible small venoarterial shunt
7	Before	90.7	98.7—100.9—103.2	Definite lung factor, probably no venoarterial shunt
	4 mos. after	91.7	100.8—103.1—105.5	Borderline, probable lung factor
8	Before	91.1	94.3—96.7—99.1	Definite venoarterial shunt
	11 mos. after	97.2	99.9—102.4—105.0	Normal

various degrees prior to valvulotomy, fell slightly in five patients (cases 1, 5, 6, 7, 8), and markedly in two (cases 2, 3). However, in no case did the pressure fall to normal.

Preoperatively, pulmonary artery pressures were low in three patients (cases 1, 2, 7), normal in two (cases 6, 8), and slightly high in two (cases 3, 5). Postoperatively, the low pressures were still low, the normal pressures were still normal, and the high pressures were slightly lower. The latter, an unexpected finding, while inexplicable at present, may have been related to another alteration especially evident in these two patients. Preoperatively, their pressure tracings showed more obviously than the others the effect of Bernouilli's principle, having normal mean pressure with very low pulse pressure just beyond the valve, and higher mean pressure and pulse pressure distally. Following valvulotomy their mean pressures were identical at the valve and beyond, and their pulse pressures were higher at the valve than peripherally.

No evidence of pulmonic insufficiency could be seen in the postoperative tracings.

There was no well defined trend in right atrial pressure.

Flow. Table 3 shows the changes in pulmonary artery and systemic flow indexes, and the data used in the calculation thereof. The changes in pulmonary artery flow were within the limits of accuracy of the method except in case 5. That patient's preoperative pulmonary artery flow was the highest in the series. Due to the marked and unsystematic variability of the right heart samples and the height of the systemic flow during the preoperative catheterization it was not clear whether there was truly a left-to-right shunt. Following surgery, the pulmonary artery flow rose markedly. The systematic increment of oxygen in the right heart samples left little doubt of the presence of left-to-right shunt. (Because of the arterial oxygen data which showed no venoarterial shunt in spite of right ventricular hypertension of systemic level, we believe this left-to-right shunt must be interatrial, though a concomitant small interventricular shunt cannot be ruled out from the right heart oxygen data.) At the postopera-

TABLE 2.—*Pressures in Pulmonic Stenosis with Intact Ventricular Septum, before and after Valvulotomy*

Pressure, mm. Hg (Mean Pressures in Parentheses)

Case No.	Right Atrium	Right Ventricle	Pulmonary Artery at Valve	Pulmonary Artery Distal
1. Pre	9/1 (4)	120/0 (53)	2/−2 (0)	2/−2 (0)
Post	1/−4 (−2)	101/0 (41)	3/−2 (1)	—
2. Pre	8/−4 (3)	65/−7 (33)	10/−1 (5)	16/4 (9)
Post	5/−8 (2)	39/−5 (14)	12/2 (9)	18/6 (12)
3. Pre	16/2 (7)	82/−6 (42)	24/6 (17)	46/5 (26)
Post	8/2 (4)	44/−6 (17)	35/15 (19)	26/11 (19)
5. Pre	0/−6 (−1)	105/9 (40)	25/16 (20)	46/13 (23)
Post	8/2 (4)	106/0 (40)	34/11 (23)	33/12 (23)
6. Pre	3/−2 (1)	57/0 (21)	24/11 (21)	19/3 (9)
Post	9/5 (6)	48/6 (28)	20/8 (13)	20/9 (13)
7. Pre	1/−4 (−1)	127/−7 (40)	1/0 (1)	5/−8 (−4)
Post	4/−6 (−2)	84/−3 (28)	14/4 (11)	—
8. Pre	2/−5 (−1)	142/2 (64)	17/−2 (8)	17/5 (10)
Post	8/0 (5)	122/−7 (58)	16/0 (15)	19/5 (11)

TABLE 3.—*Systemic and Pulmonary Artery Flow Index Data*

Case No.	Surface Area ($M.^2$)	O_2 Consumption (cc. per minute)	O_2 Capacity (vol. %)	Lung Factor	Catheterization Data, O_2 Content (vol. %)	Systemic Arterial O_2 (vol. %)	Pulmonary Venous O_2 (Calculated) (vol. %)	Flow Indexes (L /Min/M^2	
								Systemic Flow Using Sample from	Pulmonary Artery Flow Using Sample from
1. Pre	1.8	?193	23.1	.02	IVC 10.7; SVC 13.5; RA 13.8; RVM 13.9; LA 22.1, 21.2	20.7	22.7	AvVC ?1.2	RVM ?1.2
Post	1.8	193	20.1	.05	IVC 12.4; SVC 12.3; RA 12.8; RVM 13.4	18.2	19.1	RVM 2.2	RVM 1.9
2. Pre	1.2	?184	18.0	.06	IVC 13.2; SVC 13.4; RA 13.3; MPA 13.4	16.8	16.9	MPA ?4.7	MPA ?4.6
Post	1.2	184	19.1	.07	MPA 13.0	18.3	17.8	MPA 3.0	MPA 3.3
3. Pre	1.2	?222	18.8	.05	IVC 11.7; SVC 11.8; RA 12.7; RV 14.1; RVO 13.4; LV 17.5; PV 17.5	17.4	17.5	AvVC ?3.2	RVO ?4.4
Post	1.2	222	18.2	.05	IVC 12.1; SVC 12.7; RA 14.2; RVI 13.7; RVO 14.4; MPA 14.0	17.6	17.3	AvVC 3.5	MPA 5.5
5. Pre	1.6	250	19.5	.05	IVC 15.7; SVC 12.9; RA 15.6; 13.6; RVI 14.5; RVM 16.5; RVO 11.6; MPA 15.4; LPA 16.7	18.0	18.5	AvVC 4.3	MPA 5.1
Post	1.6	306	18.3	.10	IVC 13.8; SVC 13.5; RA 14.4, 14.1, 13.8, 14.6; RVM 15.3; LPA 15.6	16.8	16.5	AvVC 6.1	RVM 15.7
6. Pre	1.3	188	18.3	.01	IVC 11.7; SVC 11.4; RA 12.3; RVI 11.5, 11.8; RVO 11.9; MPA 12.0	16.8	18.1	MPA 2.9	MPA 2.3
Post	1.5	195	16.5	.06	SVC 10.1; RA 10.3; RPA 10.8	15.8	15.5	RPA 2.6	RPA 2.8
7. Pre	1.6	197	17.9	.10	IVC 14.1; SVC 12.2; RA 13.6, 11.6; RVI 12.0; MPA 12.6; RPA 12.6	16.5	16.1	RPA 3.2	RPA 3.6
Post	1.6	213	17.1	.01	RV 11.6	15.9	16.9	RV 3.2	RV 2.6
8. Pre	.72	162	16.8	.06	RA 11.4; RVO 10.9; RPA 11.0	15.5	15.8	RPA 5.0	RPA 4.7
Post	.75	152	15.9	.03	SVC 10.9; RA 12.9; RVO 11.7; MPA 11.5; RPA 12.1	16.0	15.4	RVO 4.7	RVO 5.5

Abbreviations: AvVC: average of superior and inferior venae cavae; IVC: inferior vena cava; LA: left atrium; LPA: left pulmonary artery; MPA: main pulmonary artery; RA: right atrium; RPA: right pulmonary artery; RVI: right ventricular inflow; RVM: right ventricle middle; RVO· right ventricular outflow; SVC: superior vena cava.

tive catheterization, this patient was again nonbasal with high oxygen consumption and high systemic flow. Therefore, the increment of pulmonary artery flow, though marked, should be somewhat discounted.*

A very low preoperative value for pulmonary artery flow index occurred only in a single patient (case 1). The others were borderline, normal, or actually elevated.

Valve Area. These data are shown in table 4. Two cases showed the same calculated area postoperatively, the others showed increases, the maximal increase being only three-fold.

TABLE 4.—*Pulmonary Valve Area Data*

Case No.	Systolic Ejection Period (sec./beat)	Pulse Rate, (beats/min.)	Systolic Ejection Period (sec./min.)	Pulmonary Artery Flow (cc./min.)	Pulmonary Valve Flow (cc./sec.)	Right Ventricular Systolic Ejection Mean Pressure, (mm. Hg)	Pulmonary Artery Mean Systolic Pressure, (mm. Hg)	Pulmonary Valve Area, ($cm.^2$)
1. Pre	.48	60	29	2190	76	51	0	.2
Post	.43	54	23	3380	146	49	1	.5
2. Pre	.28	72	20	5250	260	33	9	1.2
Post	.28	90	25	3830	152	20	12	1.2
3. Pre	.40	90	36	5410	150	52	26	.7
Post	.30	111	33	6720	204	22	18	2.3
5. Pre	.33	108	36	8060	226	40	23	1.2
Post	.35	90	32	25,500	810	53	22	3.2
6. Pre	.35	72	25	3080	122	39	15	.6
Post	.30	94	28	4140	147	30	9	.7
7. Pre	.44	66	29	5630	193	77	8	.5
Post	.38	72	27	4010	147	52	11	.5
8. Pre	.29	120	41	3370	81	72	10	.2
Post	.34	128	44	4110	95	43	11	.4

DISCUSSION

The relief of symptoms in these mild and moderate cases of pulmonic stenosis by an operation which appears to alter the abnormal physiology so little prompts one to wonder whether this is simply a psychotherapeutic effect. There is some evidence to suggest that the effect is physical, however. First, all seven cases reported enduring improvement, a high rate of return on a psychotherapeutic procedure. Second, the very same operative procedure is attended in severe cases by instantaneous, obvious, objective clinical improvement. A patient of ours reported elsewhere,[6] who until valvulotomy was deeply cyanotic, completely bedridden, and in congestive failure, exemplifies this. Brock[1] and others have reported similar experiences. It is difficult to believe that the postoperative anatomy of the cut valve is much different in the severe cases from that in these mild and moderate cases. Though there is no published data available on postoperative physiologic findings in severe cases, it is known that there may be marked residual physiologic evidence of stenosis in spite of unquestionable clinical benefit.[4]

* This patient warrants special mention as there was more question of the advisability of surgery in her case than in any of the others. Preoperatively, she had the largest vascular shadows on x-ray study, the highest pulmonary artery pressure and flow, and the questionable evidence of left-to-right shunt. On the other hand, right ventricular pressure was quite high, and on any exercise more active than walking, she quickly developed cyanosis and dyspnea. During the postoperative period she was maintained on digitalis because of prolonged tachycardia, which may have been due to atelectasis, as other evidences of congestive failure were lacking. Subsequently, digitalis was withdrawn and she has done very well. The postoperative physiologic measurements showing very high pulmonary artery flow and an abnormal lung factor not present preoperatively would argue that operation should not have been done. The evidence of increased exercise tolerance and removal of venoarterial shunt on the other hand are reassuring.

The working hypothesis is offered here that the stiff, cartilage-like, conical valve retains its shape after it has been split, so that it still presents an obstacle to right ventricular outflow. This is perfectly well tolerated by an individual in the mild to moderate category, who even before operation was quite comfortable at rest. Just as it required stress preoperatively to bring out symptoms, stress is required postoperatively to bring out evidence of improvement. Where before operation

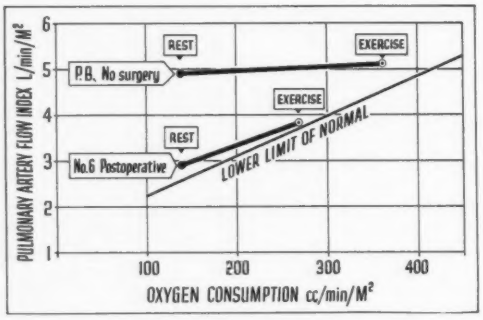

FIG. 1. Comparison of response to exercise of an asymptomatic individual (P. B.) with very mild pulmonic stenosis with one of the patients in this series (patient 6) after valvulotomy. P. B.'s pulmonary artery flow index is high but virtually fixed on exercise, while that of patient 6 is at the lower limit of normal but increased along the normal slope on exercise.

their cardiac output may have been unable to increase normally with exercise due to a fixed orifice, postoperatively the splitting of the cone would permit the temporary enlargement of the orifice during periods of increased blood flow requirement.

There has been little opportunity to test this hypothesis as the need for exercise data became apparent near the end of the present study. A comparison of data from the postoperative catheterization of patient 7 and from the catheterization of an asymptomatic individual, P. B.,* who has not been subjected to surgery, is pertinent here (fig. 1). The resting pulmonary artery flow index in case 7 was at the lower limit of normal both before and after valvulotomy. At the postoperative catheterization, the effect of exercise on pulmonary artery flow was studied. When plotted against oxygen consumption per surface area and compared with similar plots of data from a series of normal individuals during rest and exercise,[14] her response to exercise was normal. In sharp contrast, P. B. had a high normal pulmonary artery flow at rest, but with exercise the expected increase failed to occur. Though her pulmonary artery flow was fixed, she was not dyspneic nor unduly fatigued with this amount of exercise, probably because her resting output was so high that on exercise it was still within normal limits. According to our hypothesis, the difference in response of the two individuals was due to the condition of the valve. P. B.'s valve, though much less stenosed than that of patient 7, was intact, rather than split.

Dow and coworkers[15] studied the effect of exercise on cardiac output in four patients with mild to moderate pulmonic stenosis, and concluded that the cardiac output (pulmonary artery flow) responded normally to exercise. However, when their data for cardiac index are plotted against oxygen consumption per surface area, two of their four cases showed responses which fell below the lower limit of normal. Similar studies of three cases by Greene and associates,[16] when re-evaluated showed two to have normal and one subnormal exercise response. Certainly this type of study is worthy of further application wherever possible. It may be possible ultimately to state that valvulotomy effectively increases the mobility of the valve under stress even when it does not increase valve area at rest.

CONCLUSIONS

There is need for further preoperative and postoperative hemodynamic studies in mild to moderate cases of pulmonic stenosis in order to clarify the effect of valvulotomy and the indications for it. Such studies, on the basis of experience recorded here, may be expected to show little evidence of change following operation unless some additional stress is imposed.

* P. B., a 12 year old girl, had only a slight right ventricular hypertension (40/0), normal pulmonary artery pressure, and high pulmonary artery flow. There was no venoarterial nor left-to-right shunt.

Summary

Seven patients with mild to moderate pulmonic stenosis with intact ventricular septum were subjected to cardiac catheterization before and from 4 to 18 months after pulmonary valvulotomy. Despite uniform clinical improvement remarkably slight changes were observed following surgery in right ventricular pressure, pulmonary artery pressure, pulmonary artery flow, and pulmonary valve area, when measured at rest. When present preoperatively, venoarterial shunt was reduced or eliminated after operation. It was speculated that further studies, including the effect of exercise, might show that valvulotomy increases the mobility of the valve under stress even when it does not increase valve area at rest.

Acknowledgment

The technical assistance of Dorothy Pease and Betty Stout is gratefully acknowledged.

Sumario Español

Siete pacientes con estenosis pulmonar leve o moderada con septo ventricular intacto fueron sometidos a cateterismo cardíaco antes y de 4 a 18 meses después de valvulotomía pulmonar. No obstante mejoría clínica uniforme, los cambios observados después de la intervención quirúrgica en la presión ventricular derecha, presión de la arteria pulmonar, circulación de la arteria pulmonar y área valvular pulmonar fueron remarcablemente insignificantes cuando las determinaciones fueron hechas durante el descanso. Cuando un "shunt" venoarterial existía antes de la operación se redujo o se eliminó con la operación. Se especuló que otros estudios incluyendo el efecto de ejercicio podría mostrar que la valvulotomía aumenta la movilidad de la válvula bajo esfuerzo aunque no aumenta el área valvular durante descanso.

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Further Observations on the Effects of Autonomic Blocking Agents in Patients with Hypertension

II. Hemodynamic, Ballistocardiographic and Electrocardiographic Effects of Hexamethonium and Pentamethonium

By David Grob, M.D., William R. Scarborough, M.D., Albert A. Kattus, Jr., M.D., and Herbert G. Langford, M.D., with the assistance of Barbara Ziegler, Salle Lore, Grace Saltzer, and Marion Birmingham

Moderate reduction in blood pressure by intravenous hexamethonium or pentamethonium was accompanied by a decrease in stroke volume, cardiac output, and left ventricular work, and no change or an increase in peripheral resistance. Renal blood flow, filtration rate, and potassium clearance fell promptly, but returned to the original levels within one to two hours despite continued reduction in blood pressure. Sodium clearance and urine flow were reduced to a greater extent and returned more slowly. Oral hexamethonium produced some reduction in renal blood flow, and improvement in the ballistocardiogram. Oral hydrazinophthalazine diminished the effect of hexamethonium on renal blood flow.

THE GANGLIONIC blocking agents, hexamethonium and pentamethonium [bis-trimethylammonium hexane (C_6) and pentane (C_5)], have been administered to hypertensive patients orally and parenterally in an effort to reduce the blood pressure,[1-4] and to normotensive patients in order to increase blood flow to the extremities of patients with peripheral vascular disease[1, 5] and to produce postural hypotension and reduction of hemorrhage during certain operative procedures.[6] The effects of hexamethonium and pentamethonium have been very similar.[4] The studies to be reported were undertaken in an effort to determine the effect of reduction in the blood pressure, both recumbent and erect, by these compounds on the cardiac output, ventricular work, ballistocardiogram, electrocardiogram, and renal blood flow and function. Since 1-hydrazinophthalazine (Apresoline), a compound which has been reported to be a renal vasodilator,[7] has an additive effect to that of hexamethonium on the blood pressure of hypertensive patients and is frequently administered orally concurrently with hexamethonium,[3, 4, 8] the influence of this compound on the renal and ballistocardiographic effects of hexamethonium was also investigated.

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Presented in summary at the scientific session of the Twenty-fifth Annual Meeting of the American Heart Association, Cleveland, Ohio, April 19, 1952. This work was supported in part by a grant from the National Heart Institute, National Institutes of Health, U. S. Public Health Service.

Dr. Scarborough is a Howard Hughes Foundation Fellow.

Methods

The hypertensive patients who were studied varied in age from 18 to 64 (average 42) years. The patients who are classified as malignant hypertensives are those who had marked and sustained elevation of blood pressure, and some degree of renal insufficiency, papilledema, and encephalopathy.

All observations were preceded by a period of at least one week of bed rest in the hospital. Hexamethonium and pentamethonium dichloride were injected intravenously at an average rate of 3 mg. per minute until the blood pressure had fallen to normal or to levels intermediate between the original and normal, or until 100 mg. had been administered. The amount injected varied from 4 to 100 mg. (average 52 mg., or 0.74 mg. per kilogram).

Hexamethonium dichloride and hydrazinophthalazine were administered orally at four- to six-hour intervals.[4]

Cardiac output (liters per minute) was determined by measurement of oxygen uptake and arteriovenous oxygen difference (Fick), employing the cardiac catheter for obtaining mixed venous blood. During cardiac output determinations arterial blood samples were obtained, and systemic blood pressure recorded by a strain gauge and Hamilton manometer, from an indwelling cannula in the brachial artery. In a small number of patients right auricular, right ventricular, pulmonary artery, and pulmonary capillary pressures were recorded from the cardiac catheter,[9] and coronary sinus blood was obtained for estimation of coronary blood flow.[10] Total peripheral resistance was calculated from the mean blood pressure (mm. Hg.) divided by the cardiac index (liters per minute per square meter of body surface), and ventricular work (kilogram meters per minute per square meter of body surface) was calculated from the product of the mean blood pressure and cardiac index, according to the formula of Starling.[11]

Renal blood flow was determined by clearance of para-aminohippuric acid,[12] glomerular filtration rate by clearance of inulin,[12, 13] and sodium and potassium concentration in plasma and urine by flame photometry. Water loading was at a constant rate during the clearance procedures. The effect on renal blood flow and function of sitting, with the legs dangling over the sides of the bed, and of standing were determined before and after drug administration. Changes in posture were always active, rather than passive. The blood pressure was determined at frequent intervals by auscultation.

Head–foot and vector ballistocardiograms were recorded with a high-frequency bed, with simultaneous recording of electrocardiogram (lead II) and pneumogram.[14] Measurements were made of wave amplitudes and time intervals in the ballistocardiograms, which were classified as "normal," "borderline," or "abnormal" on the basis of wave form.[15] Electrocardiograms were recorded with a Sanborn Viso-Cardiette, and always included the standard limb, unipolar limb, and six unipolar precordial leads. The records were classified as "normal," "borderline," or "abnormal" on the basis of generally accepted criteria.

Results

Hemodynamic Effects

Effect of Intravenous Hexamethonium and Pentamethonium on Stroke Volume, Cardiac Output, Left Ventricular Work, and Peripheral Resistance (fig. 1). The amounts of methonium compound that were administered produced a slight reduction in systemic blood pressure in one patient, a moderate reduction in two, and a marked reduction in two. In the patient (F.M.) who had only a slight (10 per cent) reduction in mean pressure, which was still markedly elevated, there was an increase in stroke volume and cardiac output (by 50 per cent) and in left ventricular work (by 37 per cent), and a decrease in peripheral resistance (by 40 per cent). The cardiac rate was virtually unchanged. In contrast, in the four patients whose blood pressure fell to or near normotensive levels, (by 13 to 41, average 25, per cent reduction in mean pressure), there was a fall in stroke volume (by 25 to 83, average 56, per cent), in cardiac output (by 21 to 81, average 46, per cent), and in left ventricular work (by 33 to 86, average 59, per cent). Peripheral resistance was unchanged in one patient, and increased by 11, 48, and 200 per cent in the other three patients. The cardiac rate increased by 10 to 90, average 25, per cent. The reduction in stroke volume, cardiac output,

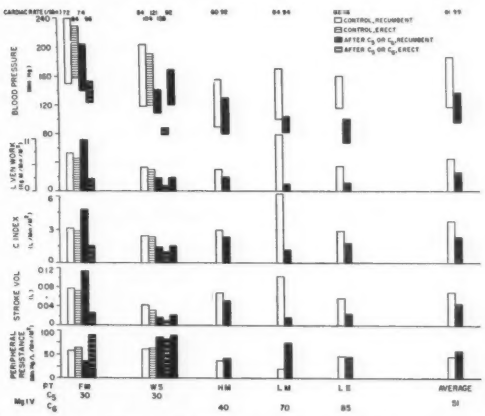

FIG. 1. Effect of intravenous hexamethonium and pentamethonium on blood pressure, left ventricular work, cardiac index, stroke volume, and calculated peripheral resistance of five patients with essential hypertension (F. M., 42 year old man, surface area 1.80 M.²; W. S., 52 year old man, 1.50 M.²; H. M., 44 year old woman, 1.85 M.²; L. M., 41 year old woman, 1.39 M.²; and L. S., 22 year old woman, 1.65 M.²), and effect of standing before and after pentamethonium in two patients. Observations in the recumbent state were carried out 15 minutes after the injection of methonium, and were repeated 30 minutes later in patient W. S. The effect of standing was noted 30 minutes after the injection of methonium.

and left ventricular work was most marked in the two patients who had the most marked fall in blood pressure, to low normal levels, and particularly in the patient (L.M.) who had an unexplained, unusually high cardiac output and low peripheral resistance prior to hexamethonium administration. The latter patient also had the most striking increase in peripheral resistance following hexamethonium.

Forty-five minutes after the administration of pentamethonium to patient W.S. and 30 minutes after the initial cardiac output determination, the diastolic pressure had returned to the original level, and the systolic to a level intermediate between the original and postinjection pressures. The initial cardioacceleration had diminished. The stroke volume, cardiac output, and left ventricular work continued to be moderately decreased, and the peripheral resistance slightly increased.

Effect of Standing. This was studied in two patients before and after pentamethonium administration. Prior to pentamethonium, standing resulted in a slight reduction in systolic pressure, a very slight increase in diastolic pressure, a slight increase in cardiac rate, a slight reduction in stroke volume (by 6 and 23 per cent), cardiac output (by 10 and 4 per cent), and left ventricular work (by 13 and 9 per cent), and a slight increase in peripheral resistance (by 12 and 3 per cent). Following pentamethonium, standing resulted in a moderate to marked reduction in systemic pressure (by 23 and 44 per cent of the control mean pressure), a marked reduction in stroke volume (by 61 and 67 per cent of control), cardiac output (by 46 and 57 per cent of control), and left ventricular work (by 74 and 51 per cent of control). The peripheral resistance increased (by 40 per cent of control) in the patient whose recumbent peripheral resistance had fallen following pentamethonium, and was unchanged in the patient whose peripheral resistance had increased following pentamethonium, remaining 32 per cent above the control value.

Effect on Right Auricular Pressure. This was measured in one patient (W.S.). The pressure was found to be 4/3 mm. Hg (recumbent) and 3/2 (erect) prior to pentamethonium and 2/0 (recumbent) and 13/11 mm. Hg (erect) following pentamethonium.

Effect on Coronary Blood Flow. This was estimated in two patients. In patient L.M., who had a marked reduction in cardiac output following hexamethonium, the recumbent coronary blood flow decreased only slightly, from 61 to 52 cc. per minute per square meter, while the calculated coronary resistance decreased from 2 to 1.7 mm. Hg per liter per minute per square meter of surface area. In patient L.S., who had a moderate reduction in cardiac output following hexamethonium, the recumbent coronary blood flow was unchanged at 85 cc. per minute per square meter while the calculated coronary resistance decreased from 1.5 to 0.9 mm. Hg per liter per minute per square meter of body surface.

Effect on Pulmonary Circulation. This was measured in one patient (H.M.). Following moderate reduction in systemic arterial pressure by hexamethonium (by 13 per cent mean pressure) there was a moderate reduction in stroke volume (by 25 per cent), in cardiac output (by 21 per cent), and in left ventricular work (by 33 per cent). There was a slight increase in systemic resistance (by 11 per cent). Pulmonary artery and capillary pressure were unchanged (6.6 and 4.2 mm. Hg mean pressure). Pulmonary resistance increased (by 29 per cent), while right ventricular work decreased (by 19 per cent).

Effect on Renal Blood Flow and Function (Tables 1 and 2)*

This was studied in four patients with benign hypertension and in one patient (R.C.) with early malignant hypertension. Two of the

* At the request of the Editor, table 1 is being omitted. This table will be furnished on request. The title of table 1 is, "Effect on blood pressure, cardiac rate, renal plasma flow, glomerular filtration rate, filtration fraction, potassium and sodium clearance, and urine flow of sitting or standing, intravenous and oral administration of hexamethonium, oral administration of hydrazinophthalazine, intravenous and oral administration of hexamethonium following hydrazinophthalazine, and sitting or standing following these drugs, in four patients with benign hypertension and one with early malignant hypertension."

former patients had normal renal blood flow and glomerular filtration rate, while the other three patients had moderately reduced renal blood flow and slightly to moderately reduced glomerular filtration. The concentration of

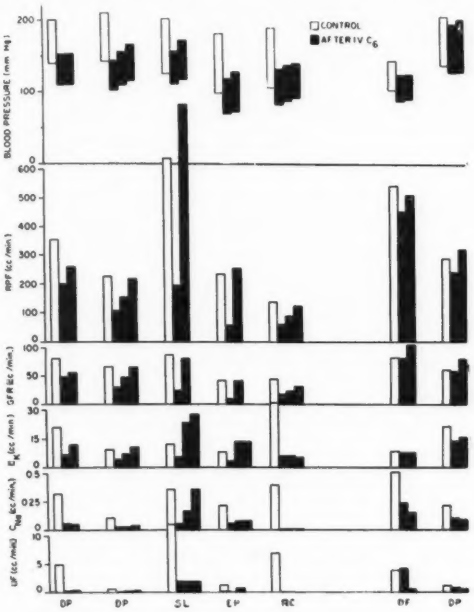

FIG. 2. Effect of intravenous hexamethonium on blood pressure (recumbent), renal plasma flow, glomerular filtration rate, potassium and sodium clearance, and urine flow of five hypertensive patients (D. P., 42 yrs., male, body surface area 1.92 M.², 100 mg. hexamethonium intravenously at rate of 3 mg. per minute (first experiment), at 15 mg. per minute (second experiment), and at 3 mg. per minute on nineteenth day of oral administration of hexamethonium, 7 Gm. four times daily (last experiment); S. L., 35 yrs., male, 2.05 M.², 75 mg.; E. P., 50 yrs., male, 1.80 M.², 18 mg.; R. C., 23 yrs., female, 1.50 M.², 80 mg.; and O. F., 26 yrs., female, 1.80 M.², 50 mg.). On the left is recorded the effect of moderate reduction in blood pressure, and on the right the effect of slight reduction. The average duration of each recorded period was 50 minutes.

blood nonprotein nitrogen was normal in the benign hypertensives at all times, while in the malignant hypertensive it was normal prior to hexamethonium administration, and increased during drug administration.

Effect of Intravenous Hexamethonium (*Figs. 2 and 3*). The intravenous administration of hexamethonium on five occasions to four patients in doses sufficient to lower the blood pressure to normal or intermediate levels, by an average reduction in mean pressure of 25 per cent, resulted in prompt reduction in renal blood flow, glomerular filtration rate, and potassium clearance by an average of 59, 60, and 63 per cent, and in sodium clearance and urine flow by an average of 83 per cent. The filtration fraction was not changed. The cardiac rate increased slightly, by an average of 4 per cent. The renal blood flow returned to the

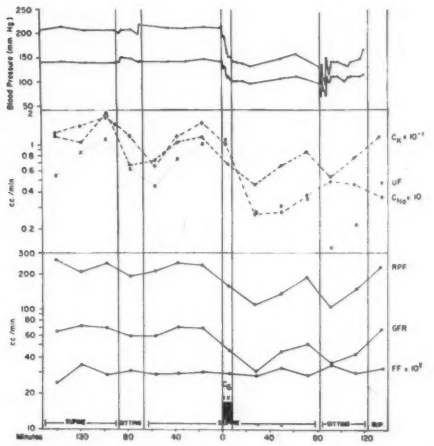

FIG. 3. Effect of the intravenous administration of 100 mg. of hexamethonium on blood pressure, renal plasma flow, glomerular filtration rate, filtration fraction, sodium and potassium clearance, and urine flow. The effect of sitting before and after hexamethonium administration is also noted. (Patient D. P.)

original levels over a period of 60 to 90 minutes after hexamethonium administration, even though the blood pressure increased but slightly during this time. The glomerular filtration rate returned a little more slowly than did the renal blood flow, and was not yet back to the original level when the renal blood flow had been restored. At that time there was a slight decrease in the filtration fraction (by an average of 5 per cent). The potassium clearance returned at approximately the same rate as did the glomerular filtration rate, while sodium clearance and urine flow were restored more slowly. Two hours after cessation of the injec-

TABLE 2.—*Per Cent Change in Mean Blood Pressure, Cardiac Rate, Renal Plasma Flow, Glomerular Filtration Rate, Filtration Fraction, Potassium and Sodium Clearance, and Urine Flow Following Intravenous and Oral Hexamethonium, Sitting or Standing before and after Hexamethonium, and Intravenous Hexamethonium before and after Oral Hydrazinophthalazine*

	Observation	No. of Pts.	% Change																									
			B.P. (mean)			Card. Rate			R P F			G F R			F F			C_K			C_{Na}			U F		
			Range		Avg.	Range		Avg.	Range		Avg.	Range		Avg.	Range		Avg.	Range		Avg.	Range		Avg.	Range		Avg.
Effect of I.V. C_6	Mod. fall in B.P.	5*	−16	−32	−25	−11	+41	+4	−43	−75	−59	−40	−74	−60	−9	+6	−2	−52	−82	−63	−73	−98	−82	−63	−96	−84
	Slight fall in B.P.	2	−7	−14	−10	+3	+34	−18			−16	−1	−5	−3	−1	+9	+4	−10	−36	−23	−59	−71	−65	−55	−87	−71
Effect of oral C_6	Sl. to Mod. fall in B.P.	2	−13	−15	−14	+17	+29	+23	−10	−32	−21	−1	−11	−6	+11	+22	+16	−2	+40	+19	−28	+124	+48	−16	+3	−7
	Mod. fall in B.P. & progression of renal dis.	1			−20			−22			+66			−88			−93			−80			−81			−73
	No fall in B.P.	1			−2			−8			+2			+4			0			+37			+15			+5
Effect of Sitting	Before I.V. C_6	4†	−8	+17	+2	+4	+16	+9	−20	−40	−30	−12	−51	−27	0	+10	+2	−37	−63	−47	−11	−42	−24	−23	−36	−28
	After I.V. C_6		−32	−43	−37	−12	+48	+8	−25	−71	−48	−18	−51	−38	−17	+7	+1	−8	−93	−58	−57	−94	−74	−75	−98	−89
	Before oral C_6	2	−8	+1	−3	+9	+16	+13	−24	−40	−32	−12	−51	−32	−17	+7	−5	−63	−37	−50	−47	−11	−29	−36	−26	−31
	After oral C_6				−17	+8	+60	+34	−66	−69	−68	−64	−70	−67	+4	−7	−2	−69	−78	−74	−79	−50	−65	−80	−76	−78
Effect of Standing	Before I.V. C_6	3	−2	+1	−1	+5	+56	+24	−43	−73	−54	−31	−67	−45	+13	+25	+20	−4	−66	−35	−49	−75	−62	−38	−8	−55
	After I.V. C_6		−21	−42	−33	−12	+56	+14	−42	−70	−58	−41	−68	−57			0	0	−79	−43	−75	−87	−82	−73	−97	−85
	Before oral C_6	1			−2			+56			−45			−31			+22			−4			−61			−38
	After oral C_6				−29			+52			−67			−66			−5			−40			−81			−97
Effect of I.V. C_6	Before hydra.	2	−16	−32	−24	+40	−6	+17	−69	−75	−72	−71	−74	−73	−7	+6	0	−52	−58	−55	−83	−73	−78	−76	−77	−77
	After hydra.		−22	−30	−26	+6	−8	−1	−20	−62	−41	−29	−68	−49	−13	−28	−20	−11	−69	−40	−90	−81	−85	−71	−59	−65

* Five observations in four patients.

† Four observations in three patients.

tion the sodium clearance and urine flow were still depressed by an average of 70 per cent. The rates of restoration of sodium clearance and urine flow varied from patient to patient, and were usually, but not always, parallel. In one patient the sodium clearance returned to the original level three hours after cessation of hexamethonium, at which time the urine flow was still depressed.

The degree of reduction of renal blood flow and function varied with the degree and rate of reduction of blood pressure. Patient D.P. received 100 mg. of hexamethonium intravenously on three occasions. Rapid injection, which produced a more rapid and slightly more marked fall in blood pressure than did slow injection, resulted in slightly greater reduction in renal blood flow and glomerular filtration rate. Injection of the drug at a time when the patient had become tolerant to orally administered hexamethonium resulted in only a very slight fall in blood pressure, a slight reduction in renal blood flow and glomerular filtration, and a moderate reduction in potassium and sodium clearance and urine flow. Similar changes occurred in another patient (O.F.), who had mild hypertension and a slight fall in blood pressure after intravenous hexamethonium. In each instance the potassium clearance was reduced to about the same degree and for the same time as the renal blood flow and glomerular filtration rate, while the sodium clearance and urine flow were reduced to a greater degree and over a more prolonged period. The effect of intravenous hexamethonium on renal blood flow and function was the same in patients with normal and with reduced renal blood flow.

Effect of Oral Hexamethonium (*Fig. 4*). In two patients (S.L. and O.F.) who had a moderate (14 per cent) reduction in mean blood pressure following oral administration of hexamethonium for 14 and 27 days, there was some reduction in renal blood flow (by 32 and 10 per cent). In another patient (D.P.), whose blood pressure did not fall, there was no change. The glomerular filtration rate was slightly reduced (by 11 per cent) in one patient (S.L.). The filtration fraction was slightly increased (by 22 and 11 per cent) in the two patients whose renal blood flow was reduced. The potassium and sodium clearance and urine flow were not significantly decreased.

In the patient with early malignant hypertension (R.C.) reduction in blood pressure to normotensive levels was accompanied by marked reduction in glomerular filtration rate, filtration fraction, potassium and sodium clearance, and urine flow, and a moderate increase in renal blood flow (tables 1* and 2). The concentration of nonprotein nitrogen in the blood increased from 33 to 64 mg. per 100 cc. Hexamethonium administration was discontinued, following which the blood pressure returned to the original hypertensive level. In spite of this, nitrogen retention progressed and the patient died in uremia 15 days later. Post mortem examination of the kidneys revealed severe arteriolosclerosis of the small cortical arteries and scattered necrotic intraglomerular arterioles.

Effect of Intravenous and Oral Hexamethonium on Postural Changes in Renal Blood Flow and Function (*Figs. 3 and 4*). Prior to hexamethonium administration, sitting for 30 minutes resulted, in four observations on three patients, in reduction in renal blood flow by an average of 30 per cent, in glomerular filtration rate by an average of 26 per cent, and in potassium and sodium clearance and urine flow by an average of 33 per cent. The filtration fraction increased by 7 per cent in three of the observations. Standing for the same period of time led to reduced renal blood flow, glomerular filtration, and clearances and urine flow by an average of 54, 45, and 51 per cent, and increase in filtration fraction by an average of 20 per cent. Sitting or standing prior to hexamethonium resulted in a very slight reduction in systolic pressure and a very slight increase in diastolic pressure. When the recumbent position was resumed for a period of 40 minutes, following sitting or standing, the renal blood flow, filtration rate, potassium and sodium clearances and urine flow returned to the original levels.

Following intravenous or oral hexamethonium administration, sitting or standing resulted in moderate or marked reduction in

* See footnote p. 354.

blood pressure to, near, or below normotensive levels. This was accompanied by reduction in renal blood flow, filtration rate, and potassium clearance to levels that were slightly lower than had occurred on sitting or standing prior

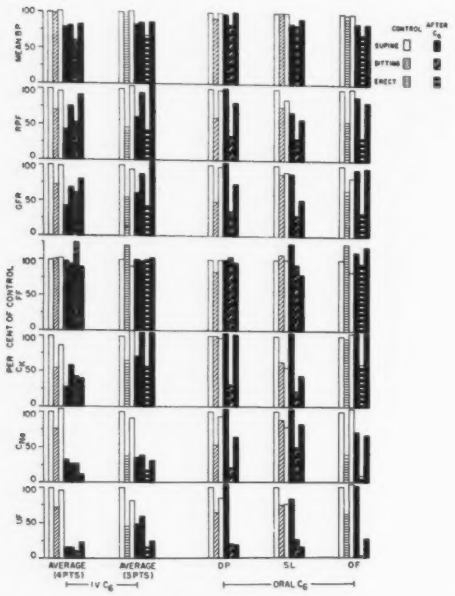

FIG. 4. Effect of intravenous and oral hexamethonium, and of sitting or standing before and after hexamethonium, on blood pressure, renal plasma flow, glomerular filtration rate, filtration fraction, potassium and sodium clearance, and urine flow of five hypertensive patients. The doses of hexamethonium administered were 18 to 100 (average 75) mg. intravenously, and 7 Gm. daily, orally for 20 days (D.P.), 2.5 Gm. daily (o) for 14 days (S.L.), and 4 Gm. daily (o) for 27 days (O.F.). The average duration of each recumbent period was 50 minutes, and of each seated or standing period 25 minutes.

to hexamethonium, and of sodium clearance and urine flow to levels that were moderately lower. In 10 observations in five patients, sitting and standing after intravenous or oral hexamethonium resulted in reduction in mean blood pressure by an average of 30 per cent (sitting) and 32 per cent (standing) of the control recumbent values, in renal blood flow by 55 and 60 per cent, in glomerular filtration rate by 48 and 59 per cent, in potassium clearance by 63 and 42 per cent, in sodium clearance by 71 and 82 per cent, and in urine flow by 85 and 88 per cent. The sodium clearance and urine flow were reduced to a greater degree than the renal plasma flow and glomerular filtration rate, in contrast to the changes that occurred on sitting or standing prior to hexamethonium. In addition, when the recumbent position was resumed the sodium clearance and urine flow did not return to the recumbent levels as rapidly as prior to hexamethonium. The filtration fraction did not change significantly on standing, in contrast to the increase that occurred prior to hexamethonium. On the other hand, the filtration fraction increased on sitting to a greater extent than prior to hexamethonium. The slight to moderate cardioacceleration that occurred on sitting or standing was approximately the same before and after hexamethonium. The level to which renal blood flow and function fell during postural hypotension was approximately the same after intravenous and oral hexamethonium, and was the same when the recumbent blood pressure was elevated as when it had been reduced to normotensive levels by hexamethonium.

Effect of Oral Hydrazinophthalazine. The oral administration of 600 mg. of hydrazinophthalazine daily to two patients for five and eight days resulted in a very slight (8 per cent) increase in renal blood flow (table 1, d–g*). Glomerular filtration rate increased by 26 per cent in one patient, and decreased by 49 per cent in the other patient, whose filtration fraction also decreased. The potassium and sodium clearance and urine flow were not significantly changed. The mean systemic pressure was reduced by 12 per cent in one patient, and was not altered in the other.

Hydrazinophthalazine administration had no significant effect on the slight reduction in renal blood flow and glomerular filtration rate that occurred following oral hexamethonium, and no effect on the reduction in renal blood flow and function that occurred on sitting

* See footnote p. 354.

or standing, either before or after the oral or intravenous administration of hexamethonium. It did appear to diminish to some extent the degree of reduction in renal blood flow, and to a lesser extent in glomerular filtration rate, that occurred immediately after the intravenous administration of hexamethonium (table 2). Whereas there was no alteration in the filtration fraction immediately after intravenous hexamethonium, there was a 20 per cent decrease when hexamethonium was administered following hydrazinophthalazine. There was no change, however, in the reduction in potassium and sodium clearance, and in urine flow, that occurred following intravenous hexamethonium. Although the amount of hexamethonium injected was less in one patient during hydrazinophthalazine administration, the reduction in blood pressure was actually slightly greater.

Effect on the Ballistocardiogram

Observations were carried out in 19 hypertensive patients (13 benign and 6 malignant), whose ages ranged from 18 to 64 (average 42) years. The ballistocardiogram was normal in only one patient, who was the youngest in the group (18 years) and who had the shortest known duration of hypertension (nine months). Sixteen patients had abnormal ballistocardiograms, and in two patients the records were considered to be borderline. In 11 of the abnormal records two characteristic alterations were noted. There were relatively deep, broad, slurred or doubled K waves, and small and distorted or absent I and J waves in the conventional head-foot record. The I and J waves were nearly normal in one of the vector records, suggesting rotation of the IJ axis. In some patients the L wave was unusually prominent. Aside from these alterations there was considerable variation in form in the abnormal ballistocardiograms. In the other five abnormal records the form was so abnormal that identification of specific waves was impossible. In seven patients the amplitude was abnormally low.

Effect of Intravenous Methonium (Tables 3 and 5).* Twelve patients were administered hexamethonium and two pentamethonium, in doses of from 4 to 100 mg. (average 51 mg.). These doses lowered the blood pressure to

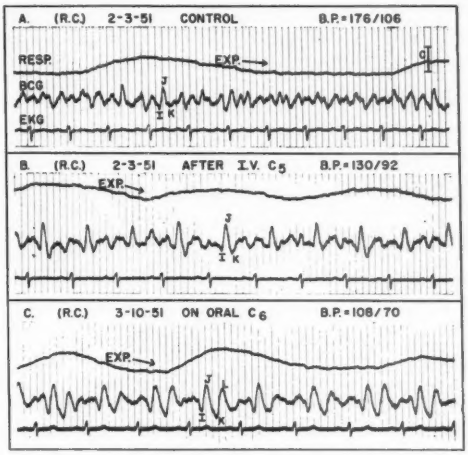

FIG. 5. Improvement in ballistocardiogram of a patient with early malignant hypertension (R. C., age 23) following reduction in blood pressure by intravenous pentamethonium and by oral hexamethonium. (*A*) Control. Ballistocardiogram is low in amplitude and grossly abnormal in form, with only an occasional normal complex. (*B*) After intravenous pentamethonium. Amplitude of ballistocardiogram is increased and complexes are more clearly defined. (*C*) During oral hexamethonium. Further increase in amplitude and improvement in form. Although the L waves are prominent, the record is within normal limits.

(In this figure, and in figures 6–8, the upper tracing on each record is the pneumogram (Resp.), the middle tracing is the ballistocardiogram (BCG), and the lower tracing is the electrocardiogram (EKG—lead II). Vertical time lines are 0.1 second apart. The bracketed vertical line (C) in the upper right hand corner of the top record represents 1 cm. calibration, and applies to all records in each figure.)

normal in five patients, to levels slightly above normal in four, and to levels intermediate between the original hypertensive and

* At the request of the Editor, table 3 is being omitted. This table will be furnished on request. The title of table 3 is, "Effect of intravenous hexamethonium and pentamethonium on the electrocardiogram and the ballistocardiogram."

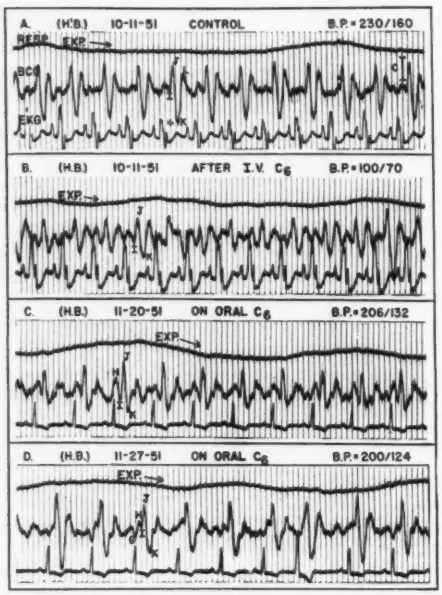

FIG. 6. Slight improvement in ballistocardiogram of a patient with malignant hypertension (H. B., age 37) following reduction in blood pressure by intravenous hexamethonium, and more marked, though temporary, improvement in ballistocardiogram, with improvement in electrocardiogram, following lesser reduction in blood pressure by oral hexamethonium. (*A*) Control. Ballistocardiogram is abnormal, showing no definite I waves, and unusually deep K and prominent L waves. Electrocardiogram shows left bundle branch block. (*B*) After intravenous hexamethonium, there has been reduction in amplitude of K and L waves. The I waves are distorted and variable, but are deeper than in the control record. (*C*) After 15 days of oral hexamethonium and hydrazinophthalazine, ballistocardiogram is markedly improved and is now within normal limits, even though the blood pressure is considerably above normal, though lower than the original level. Electrocardiogram reveals that the bundle branch block has been replaced by left ventricular "strain" pattern. (*D*) After 22 days of the same medication the ballistocardiogram has reverted to the abnormal form seen in the control record, despite further slight reduction in the blood pressure. The tracing again shows small or absent I waves and deep K waves. The electrocardiogram has not reverted to the control form, indicating that bundle branch block was not responsible for the ballistocardiographic abnormality of the control record, and that disappearance of the conduction defect was not responsible for ballistocardiographic improvement (C).

normal in five. One patient received hexamethonium on two occasions, once in sufficient amount to lower the blood pressure to low normal, and once to an intermediate level. The average blood pressure of the 14 patients studied was 222/131, and following methonium 149/100. There was no alteration in the average cardiac rate.

Following methonium administration there was improvement in the ballistocardiogram in six patients (figs. 5 and 6), and in three of these the record became normal. Improvement in form often consisted of diminution in the abnormally deep K wave, and increase in the abnormally low I and J waves (fig. 6). In three patients the records became more abnormal, with almost complete disappearance of the systolic complexes (fig. 7), and in five patients there was no change. In six patients there was a decrease in amplitude of the ballistocardiogram, accompanied in two by improvement in form, in three by no change in form, and in one by greater abnormalities in form. In one patient there was a striking increase in amplitude, accompanied by improvement in form. In most patients there were changes in the timing of the ballistic systolic waves, consisting of an increase in the duration of the Q-I, Q-J, and Q-K intervals, by a mean of 0.03, 0.03, and 0.04 second, respectively.

The effect of methonium injection on the ballistocardiogram could not be correlated with the precise degree of reduction in the blood pressure. Improvement occurred after reduction to, or near, normotensive levels in four patients, and to an intermediate level in two. The ballistocardiogram became more abnormal after reduction in pressure to near normal in one patient, and to an intermediate level in two. There was no change after reduction in pressure to normal in two patients, to near normal in two, and to intermediate levels in two. One patient did have improvement in the ballistocardiogram after reduction in pressure to 100/70 mm. Hg (fig. 6), and this improvement was not maintained when the blood pressure rose to an intermediate level. There was likewise no correlation with the level of systolic or diastolic pressure prior to drug

administration, or with the benign or malignant characterization of the hypertension. All four patients with malignant hypertension (ages 19 to 45, mean 30, years) had improvement in the ballistocardiogram after methonium administration. There did appear to be some variation in degree of ballistic improvement with the age of the patient, and perhaps with the duration of the hypertension. If the 18 year old patient whose control ballistocardiogram was normal and who had no change after methonium is excluded, the average age of the patients whose ballistocardiograms improved was 34 years (range 19 to 47 years), of those in whom there was no change 48 years (range 46 to 50 years), and of those whose ballistocardiograms became worse 52 years (range 47 to 56 years).

Following Oral Administration (*Tables 4* and 5*). Seven patients were administered 0.5 to 6 (mean 2.7) Gm. of hexamethonium per day for 9 to 21 (mean 16) days, and six patients were given similar doses of hexamethonium together with 100 to 600 mg. (mean 310) of hydrazinophthalazine per day, five for 15 to 22 (mean 19) days and one for 252 days. In three patients the ballistocardiogram was recorded during both hexamethonium and combined drug administration. Five patients had been studied previously following the intravenous injection of hexamethonium. At the time ballistocardiograms were obtained during oral administration of hexamethonium the blood pressure had been reduced to, or near, normal in three patients, to intermediate levels in three, and only slightly in one. The average blood pressure fell from 211/131 to 162/97. At the time the ballistocardiograms were obtained during combined drug administration the blood pressure had fallen to near normal in two patients, and to intermediate levels in four. The average blood pressure fell from 226/142 to 176/103. There was no significant change in cardiac rate. During the first week of drug administration the blood pressure was, in most patients, slightly to moderately lower than at the time ballistocardiograms were obtained.

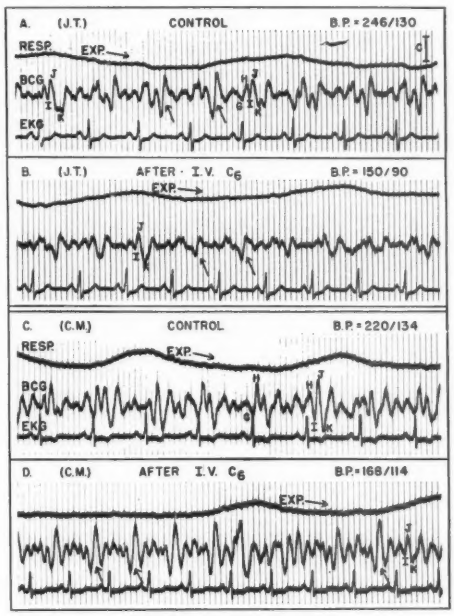

FIG. 7. Increased abnormality of ballistocardiogram of two patients with essential hypertension following reduction in blood pressure by intravenous hexamethonium. (*A*) Control (J. T., age 49). Ballistocardiogram is grossly abnormal; there are no normal systolic complexes present. The record is dominated by large early diastolic deflections (arrows). (*B*) After intravenous hexamethonium. There is marked reduction in amplitude of both systolic and diastolic waves. (*C*) Control (C. M., age 47). Ballistocardiogram abnormal, although a few normal complexes are present. G and H waves are large. (*D*) After intravenous hexamethonium. Ballistocardiogram form is more abnormal. Systolic waves can only rarely be identified, and there are very large, clearly defined mid-diastolic waves. The diastolic complexes resemble normal systolic complexes and could be mistaken for them if the electrocardiogram were not recorded simultaneously.

During drug administration there was distinct improvement in the ballistocardiogram of all 10 patients, and in four of these the record became normal (figs. 5, 6, and 8). The nature of the change in ballistic form varied

* At the request of the Editor, table 4 is being omitted. This table will be furnished on request. The title of table 4 is, "Effect of Oral Hexamethonium and Hexamethonium plus Hydrazinophthalazine on the Electrocardiogram and the Ballistocardiogram."

to some extent with the form of the control record. Abnormalities of the K wave tended to decrease or disappear (figs. 6 and 8). I and J waves generally became larger and more clearly defined (figs. 5, 6, and 8), the mean IJ amplitude increasing by 5 mm. or more in 7 of the 10 patients. Prominent H waves and abnormal diastolic waves, when present, tended to diminish. There was an increase in amplitude, at times marked, in six patients. There was no significant change in the timing of the ballistic waves. The effect of combined drug administration was, in general, similar to the effect of hexamethonium alone.

Recordings were obtained on two or three occasions during drug administration in four patients. In one patient there was further improvement in the second and third records as the blood pressure was progressively lowered to near normal. In one patient slight improvement persisted, and in two patients the second record reverted toward the control, even though the blood pressure continued to be moderately reduced (fig. 6, *C* and *D*).

The degree of ballistic improvement was greater in the younger patients, and was least in the two patients who were over 50 years of age. The degree of improvement could not be related to the degree of reduction in blood pressure, or to the benign or malignant characterization of the hypertension. Both slight and marked improvement occurred following reduction in blood pressure to normal and following reduction to intermediate levels. There were not sufficient observations to ascertain the relation of the degree of ballistic improvement to the duration of the reduction in blood pressure, or to the clinical course of the patient. All the patients whose ballistocardiogram became normal showed improvement in many of the signs and symptoms attributable to hypertension, including those attributable to left ventricular decompensation, concomitant with the reduction in blood pressure. However, the two oldest patients, who had only slight ballistic improvement, despite moderate to marked reduction in blood pressure, had comparable symptomatic im-

TABLE 5.—*Summary of the Effect of Hexamethonium (or Pentamethonium) on the Electrocardiogram and Ballistocardiogram*

1. Effect of intravenous administration:

ECG					BCG				
Control		After I.V.C.$_6$			Control		After I.V.C.$_6$		
	No.	Improved	Worse	Unchanged		No.	Improved	Worse	Unchanged
N*	1	0	0	1	N	1	0	0	1
B*	3	1	1	1	B	2	2	0	0
A*	10	4	2	4	A	11	3	3	5
Total	14	5	3	6	Total	14	5	3	6

2. Effect of prolonged oral administration (with or without hydrazinophthalazine):

ECG					BCG				
Control		On Oral C$_6$			Control		On Oral C$_6$		
	No.	Improved	Worse	Unchanged		No.	Improved	Worse	Unchanged
N	1	1	0	0	N	0	0	0	0
B	2	2	0	0	B	1	1	0	0
A	7	4	1	2	A	9	9	0	0
Total	10	7	1	2	Total	10	10	0	0

* N = normal record, B = borderline, and A = abnormal.

provement. The degree of ballistic improvement could not be related to the rate of development of tolerance to the antihypertensive effect of the drugs. Improvement in the ballistocardiogram was more marked after prolonged oral than after acute intravenous administration of hexamethonium in four of the five patients who received the drug by both routes.

Effect on the Electrocardiogram

Electrocardiograms were recorded simultaneously with the ballistocardiogram. Of the 19 patients who were studied, 13 had abnormal electrocardiograms, four had tracings which were considered to be borderline, and two had normal records. In 12 of the abnormal electrocardiograms a left ventricular "strain" pattern was present, and in the other abnormal record there was left bundle branch block. In the four borderline electrocardiograms there were minor T-wave changes, and, in three of the four, left axis deviation.

Effect of Intravenous Methonium (Tables 3 and 5).* Following hexamethonium or pentamethonium there were minor changes in the electrocardiogram in seven patients, and no change in seven. In four patients there was some improvement in the electrocardiogram, consisting of S-T segment and T-wave changes and, in only one of these, some shift of the QRS axis toward normal. In no instance, however, did the electrocardiogram become normal. In three patients the pre-existing S-T segment and T-wave changes were accentuated.

Effect of Oral Hexamethonium (Tables 4† and 5). There was moderate improvement in the electrocardiogram of two patients, consisting of disappearance of left ventricular "strain" pattern in one (fig. 8) and replacement of left bundle branch block by left ventricular strain in the other (fig. 6). In four patients there was minor improvement, consisting mainly of S-T segment and T-wave changes, and in four patients there was no change. None of the abnormal electrocardiograms became normal, but one record which had been classified as borderline became normal, and one abnormal record became borderline. Changes in QRS axis were insignificant. The effect of hexamethonium plus hydrazinophthalazine appeared to be the same as of hexamethonium alone. The degree of improvement in the electrocardiogram was somewhat greater after prolonged oral than after acute intravenous administration of hexamethonium in three of the five patients who received the drug by both routes.

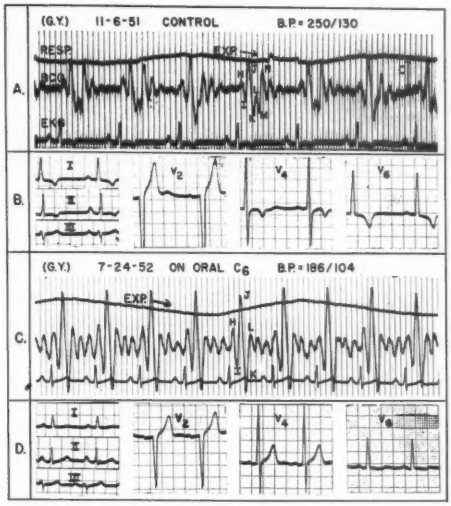

FIG. 8. Improvement in ballistocardiogram and electrocardiogram of a patient with essential hypertension (G. Y., age 47) following reduction in blood pressure by oral hexamethonium. (*A*) Control ballistocardiogram, showing short I waves and an unusual late systolic-early diastolic pattern. There are deep K waves and very short L waves which never return to the base line. The M waves are deep, at times deeper than the K waves, and occasionally fuse with the K waves to form large, broad footward waves. The N waves are quite prominent and at times equal the J waves in height. (*B*) Control electrocardiogram, showing left ventricular "strain" pattern. (*C*) Ballistocardiogram during oral hexamethonium is normal. IJ amplitude has doubled and the unusual KLMN wave pattern has disappeared. (*D*) Electrocardiogram during oral hexamethonium shows disappearance of left ventricular "strain" pattern. T waves are low in leads I and V_6.

The incidence or degree of improvement that occurred following administration by either route could not be correlated with the precise degree of reduction in the blood pressure, with the age of the patient, known duration of hypertension, original blood pressure, or malig-

* See footnote p. 359.

† See footnote p. 361.

nant versus benign character of the hypertension. There was insufficient data to establish any correlation with the duration of reduction in blood pressure or with the clinical course, although it is of interest that the only patient who had disappearance of a left ventricular strain pattern had the longest period of reduction in blood pressure. Although the changes in the ballistocardiogram that occurred following methonium were much more striking than the changes in the electrocardiogram, the two usually changed in the same direction. In only two instances did one record become worse when the other improved.

Discussion

Hemodynamic Effects

The basis of hypertension is increased systemic peripheral resistance, perhaps due, in part, to increased sympathetic vasoconstrictor tone.[12] In uncomplicated hypertension the cardiac output is usually normal,[12] but because of the increased systemic blood pressure the blood flow to the heart,[10] brain,[16] and extremities[17] is usually near normal until fixed vascular changes ensue, while that to the kidneys is usually slightly to moderately reduced.[12] In the management of hypertensive disease the goal is reduction of blood pressure without serious impairment of blood flow to the vital organs. The reduction in blood pressure produced by hexamethonium or pentamethonium is believed to be due to reduction in sympathetic vasoconstrictor tone resulting from inhibition of ganglionic conduction, though the location of the areas where vasodilatation occurs, other than the skin, is not known. It is possible that the splanchnic bed may be important in this regard. Following slight reduction in blood pressure by intravenous methonium, the increased cardiac output that occurred is compatible with the maintenance of blood flow to most areas. Following moderate or marked reduction in blood pressure, on the other hand, the reduction in cardiac output that occurred is compatible with reduction in blood flow to some areas. This would be expected to be most marked wherever fixed vascular changes are present. Clinical evidence suggestive of reduction in renal, coronary, cerebral, and retinal blood flow following reduction in the blood pressure by hexamethonium has occurred in some patients and has been more frequent and more marked in patients with malignant hypertension than in those with benign hypertension.[4]

The reduction in cardiac output produced by methonium is most likely due to decreased venous return resulting from the pooling of blood in peripheral areas of vasodilatation. The decrease in right auricular pressure that occurred is compatible with this, but may also have been due to decreased venomotor tone. A direct depressant effect of methonium on the heart cannot be entirely excluded, though such an effect has not been demonstrated. The lack of change, or increase in the calculated peripheral resistance reflects the greater reduction in cardiac output than in mean arterial pressure. Since the pulmonary artery and capillary pressures did not change, and the calculated pulmonary resistance increased, pooling of blood probably did not occur in the pulmonary circulation. Werkö and his associates[18] observed a reduction in cardiopulmonary blood volume in three hypertensive patients following reduction in blood pressure by hexamethonium, even though pulmonary artery and capillary pressures fell to some extent. The systemic peripheral resistance was reported to have decreased in these patients, and the cardiac output to have decreased in two of the three.

Since the estimated coronary blood flow was unchanged or only slightly reduced, and the calculated coronary resistance reduced following lowering of the blood pressure by hexamethonium, it would appear that the coronary vessels were under resting sympathetic tone, and that coronary vasodilatation occurred immediately after hexamethonium injection in the patients studied. Vasodilatation apparently does not always occur, since electrocardiographic changes compatible with reduced coronary blood flow occurred following reduction in blood pressure by hexamethonium in two patients with malignant hypertension,[4] and fatal myocardial infarction, has been reported.[19]

The postural hypotension which occurs as

a result of inhibition of reflexly mediated peripheral vasoconstriction by the ganglionic blocking action of methonium is associated with a marked reduction in stroke volume and cardiac output, and either no change or an increase in calculated peripheral resistance. The reduction in stroke volume and cardiac output are probably the result of decreased venous return following pooling of blood in the peripheral circulation. Whatever the cause, the reduction in cardiac output that occurs during postural hypotension would be expected to result in decreased blood flow to some areas. The frequent occurrence of syncope is, of course, a reflection of decreased cerebral blood flow. The need for study of the effect of hexamethonium-induced postural hypotension on blood flow to the vital organs is evident, particularly since the recommendation has been made[2] that hypertensive patients receiving hexamethonium sleep in a semi-recumbent position to facilitate reduction of their blood pressure throughout 24 hours. The administration of hydrazinophthalazine usually produces some increase in cardiac rate, and intravenous administration has been reported to produce an increase in stroke volume and cardiac output.[7] It is possible that the concurrent administration of sufficient hydrazinophthalazine may prove capable of reducing the depression of cardiac output that may follow hexamethonium.

The reduction in renal blood flow that occurred immediately following reduction in blood pressure by intravenous hexamethonium indicates that renal vasodilatation did not occur at that time, while the gradual recovery of renal blood flow, long before the blood pressure, points to the gradual occurrence of renal vasodilatation. Similar changes in renal blood flow were observed by Smith following spinal anesthesia, and were interpreted by him as indicating that the renal vascular tree is not under resting sympathetic vasoconstrictor tone, but is capable of autonomous regulation of tone.[20]

The reduction in glomerular filtration rate and potassium clearance that occurred paralleled in general, and probably depended upon, the reduction in renal blood flow. The reduction in sodium clearance and urine flow, on the other hand, exceeded and was more prolonged than the reduction in renal blood flow and glomerular filtration rate. Following reduction in blood pressure, the latter changes are known to be accompanied by increased tubular reabsorption of sodium and water,[21] but the relative roles of decreased filtration rate and blood flow, and of release of a circulating antinatruretic and antidiuretic substance are not known.

In the patients with benign hypertension reduction in blood pressure by *oral* hexamethonium resulted in some reduction in renal blood flow and, to a lesser extent, in glomerular filtration rate, but no observed decrease in potassium or sodium clearance or in urine flow. However the occurrence of hemodilution and of increased extracellular fluid volume in some patients following reduction in blood pressure by oral hexamethonium[4] suggests that sodium and water retention may occur. In the patient with malignant hypertension who was studied, reduction in blood pressure by oral hexamethonium was followed by marked reduction in glomerular filtration rate, filtration fraction, potassium and sodium clearance and urine flow, moderate increase in renal blood flow, and increased nitrogen retention which later progressed to uremia in spite of discontinuation of hexamethonium and return of hypertension. The reduction in blood pressure induced by hexamethonium in this patient was apparently accompanied by a rapid increase in renal damage, with irreversible changes. The functional alterations that were observed suggest that, at the time the studies were carried out, diversion of blood to extraglomerular shunts may have occurred, but the relation of this to the ganglionic blocking effects of hexamethonium, or to the reduction in blood pressure and damage to glomerular arterioles (observed post mortem), is not clear.

The reduction in renal blood flow, glomerular filtration rate, potassium and sodium clearance and urine flow that occurred in the hypertensive patients on sitting or standing prior to drug administration was greater than that described in normal subjects.[22] This was true of hypertensive patients with normal renal blood flow, as well as of those with reduced renal blood flow. The postural reduction in

renal blood flow is probably due to reflexly mediated renal vasoconstriction, since the cardiac output falls very slightly, if at all, on standing or sitting. The occurrence of more marked reduction in hypertensive patients than in normal subjects may reflect more marked peripheral vasoconstriction required to maintain the elevated blood pressure in the erect position. The increase in filtration fraction that occurs in both hypertensive and normal subjects on standing indicates that efferent vasoconstriction may be greater than afferent. The reduction in the various renal functions was equal to the reduction in renal blood flow, indicating that the latter was responsible. Following hexamethonium administration, sitting or standing resulted in only slightly greater reduction in renal blood flow, glomerular filtration and potassium clearance than had occurred prior to hexamethonium, in spite of the reduction in blood pressure and cardiac output. Since reflexly mediated vasoconstriction is inhibited by hexamethonium, the reduction in renal blood flow would appear to be due to the reduction in blood pressure and cardiac output. There was no change in the filtration fraction on standing following hexamethonium, but the filtration fraction did increase during sitting. The sodium clearance and urine flow fell to a greater degree on sitting or standing following hexamethonium than did the renal blood flow, filtration rate, and potassium clearance, and whereas the latter returned to the original levels when the patient resumed the recumbent position, the former, particularly the urine flow, remained depressed. The reduction in sodium clearance and urine flow would appear to be the result not only of reduction in glomerular filtration rate and renal blood flow, but also of some additional antidiuretic and antinatruretic effect of reduction in the blood pressure.

Intravenously administered hydrazinophthalazine has been reported to increase stroke volume, cardiac output, and renal blood flow in many hypertensive patients.[7] Oral administration to two patients, however, had little or no effect on renal blood flow or function, or on the effect of sitting or standing on renal blood flow and function either before or after intravenous or oral hexamethonium. It did appear to diminish the effect of intravenous hexamethonium on renal blood flow, and, to a lesser extent, on glomerular filtration rate. Whether this was mediated through alteration of the effect of hexamethonium on cardiac output, or through more rapid renal vasodilatation following reduction in blood pressure remains to be determined. The relation of this "protective" influence of hydrazinophthalazine to the much lower incidence of renal insufficiency observed during combined drug administration than during hexamethonium administration[4] also remains to be determined. Hydrazinophthalazine did not diminish the marked reduction in sodium clearance and urine flow which followed intravenous hexamethonium. This suggests that the antinatruretic and antidiuretic effect of reduction in blood pressure by hexamethonium may be due in part to the release of a circulating substance by some other organ than the kidney, since it was not entirely dependent on reduced renal blood flow.

Ballistocardiographic and Electrocardiographic Effects

The high incidence and nature of the ballistocardiographic abnormalities observed in the hypertensive patients studied are in accord with the findings of other observers.[23-25] The cause of these abnormalities is not clear, though it is believed that the more advanced changes are due to inability of the heart to eject blood with normal force, and that the deep K wave and "late downstroke" patterns may be due to ejection of blood with maximum velocity much later in systole by the chronically overburdened hypertensive heart than by the normal heart.[26] The relative importance of increased peripheral resistance and of other alterations in cardiovascular function in the development of abnormalities in ballistic form is not clear. While deep K and short I waves may occur following compression of the abdominal aorta,[27] the production of a transient increase in general peripheral resistance and in blood pressure by the administration of pressor agents to normal subjects does not

result in abnormal ballistic form, though it may result in a change in amplitude.[28,29]

Improvement in the ballistocardiogram, presumably reflecting improvement in the ejection of blood by the heart, was more common and more striking after prolonged reduction in the blood pressure by oral hexamethonium or hexamethonium plus hydrazinophthalazine than after more acute reduction by intravenous hexamethonium. This was also true of the less striking improvement in the electrocardiogram. Worsening of the ballistocardiogram occurred only after intravenous administration of drug, and in the case of the electrocardiogram was more frequent after intravenous than oral administration. It is not clear whether these differences are due to the more rapid reduction in blood pressure after intravenous than after oral administration of drug, or to the more prolonged reduction in blood pressure during oral administration. However, it is of interest that worsening of the ballistocardiogram has been reported to occur immediately after sympathectomy and improvement several months later.[25] Improvement in the ballistocardiogram has also been reported to have occurred in a few instances following reduction of blood pressure by an antipressor kidney extract,[28] and in two patients following veratrum viride.[25]

There was usually an increase in the amplitude of the ballistocardiogram following oral hexamethonium, whereas a decrease in amplitude was more common after intravenous administration. The ballistic changes could not be correlated with the degree of reduction in blood pressure, and the abnormalities of ballistic form that were present precluded calculation of cardiac output from these tracings. There was, in addition, an increase in the average Q-I, Q-J, and Q-K intervals after intravenous but not after oral drug. It is possible that the delay in the systolic waves may reflect a decrease in pulse-wave velocity, although the intervals were not unusually short prior to hexamethonium.

The cause of the differences between the effects of intravenous and of prolonged oral administration is not known, but the occurrence of differences suggests that the hemodynamic effects of the drug may not be the same in each instance, and that it may not be possible to predict the effects of prolonged oral administration from those observed after intravenous injection.

The degree of ballistocardiographic improvement following reduction in blood pressure by hexamethonium was much greater in patients under 50 years of age than in those over 50. This difference may be due to the fact that the ballistocardiogram is frequently abnormal even in clinically normal persons over 50 years of age.[15] Such factors as coronary artery disease, aortic atherosclerosis and minimal pulmonary emphysema may be responsible for ballistocardiographic changes, and may limit the degree of ballistic improvement following reduction in the blood pressure of older hypertensive subjects.

Summary

1. Slight reduction in blood pressure by intravenous hexamethonium or pentamethonium was accompanied by an increase in stroke volume, cardiac output, and left ventricular work, and a decrease in calculated peripheral resistance. Moderate or marked reduction in blood pressure was accompanied by a decrease in stroke volume, cardiac output, and left ventricular work, and either no change or an increase in peripheral resistance. When the patient stood up, there was a further reduction in blood pressure, stroke volume, cardiac output, and left ventricular work, and either no change or an increase in peripheral resistance. The right auricular pressure decreased following methonium while the patient was recumbent, but increased when the patient stood up. Coronary blood flow was unchanged or slightly reduced following methonium, while coronary resistance decreased. Pulmonary artery and capillary pressure was unchanged, while pulmonary resistance increased slightly.

2. Moderate reduction in blood pressure by intravenous hexamethonium was followed by prompt reduction in renal blood flow, glomerular filtration rate, and potassium clearance, and, to a greater extent, in sodium clearance and urine flow. The renal blood flow returned

to the original levels over a period of 60 to 90 minutes, even though the blood pressure increased but slightly. Glomerular filtration rate and potassium clearance increased a little more slowly, and sodium clearance and urine flow considerably more slowly. Reduction in blood pressure by oral hexamethonium was accompanied by some reduction in renal blood flow, and, to a lesser extent, in glomerular filtration rate. Sitting or standing following intravenous or oral hexamethonium resulted in reduction in renal blood flow, filtration rate, and potassium clearance to levels that were slightly lower than had occurred on sitting or standing prior to hexamethonium, and of sodium clearance and urine flow to levels that were moderately lower. The oral administration of hydrazinophthalazine resulted in only a very slight increase in renal blood flow, but it did appear to diminish the degree of reduction in renal blood flow that occurred following the intravenous administration of hexamethonium.

3. Following the intravenous administration of hexamethonium or pentamethonium there was improvement in the ballistocardiogram in 6 of 14 patients, and increased abnormality in three patients. There was slight improvement in the electrocardiogram in four patients, and increased abnormality in three. Following the oral administration of hexamethonium or of hexamethonium plus hydrazinophthalazine there was improvement in the ballistocardiogram in each of 10 patients, and an increase in amplitude in six of these. There was moderate improvement in the electrocardiogram in two patients, and minor improvement in four. The degree of ballistic improvement that occurred was greater in the younger patients.

Acknowledgments

The authors are indebted to Drs. A. McGehee Harvey and Elliott V. Newman for their advice and encouragement, and to Drs. Richard J. Bing and Henry T. Bahnson for their generous assistance in the studies that involved cardiac catheterization. Dr. Donald S. Searle of Burroughs Wellcome Company, Tuckahoe, N. Y., provided the hexamethonium (Hexameton) that was employed, and Dr. Jock L. Graeme of Ciba Pharmaceutical Company, Summit, N. J., provided the hydrazinophthalazine (Apresoline).

Sumario Español

Reducción moderada de la presión arterial con hexamethonium o pentamethonium intravenoso fué aconpañada por un decremento en emisión sistólica, en producción total cardíaca y en trabajo del ventrículo izquierdo, y ningún cambio o un incremento en resistencia periférica. La circulación renal, promedio de filtración y depuración del potasio disminuyó prontamente, pero volvió a su nivel original en una o dos horas no obstante continua reducción en presión arterial. La depuración del sodio y producción de orina fueron reducidas mas marcadamente y volvieron a su nivel original más lentamente. Hexamethonium oral produjo alguna reducción en circulación renal y mejoría en el balistocardiograma. Hydrazinophthalazine oral disminuyó el efecto del hexamethonium en la circulación renal.

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The Kinetocardiogram

II. The Normal Configuration and Amplitude

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An analysis of the patterns and amplitudes of the precordial movements is presented. Normal young adult subjects had three types of patterns. Type I occurred in 78 per cent, type II in 14 per cent, and type III in 8 per cent of the subjects studied. The variations of the kinetocardiogram from apex cardiograms and pneumocardiograms are discussed.

IN A PRECEDING communication, a method of recording chest-wall movements and the general configuration of the normal pattern was described. The purpose of this paper is to present a more detailed analysis of the normal kinetocardiogram.

Methods

The procedure for recording the precordial movements was described in the previous publication.[1] Records were taken from KV_1 through KV_5, and KV_{3R}. (KV_{3R} is in the same location as KV_3, except for being located on the anterior right side of the chest.) KV_1, KV_2, etc., are used to denote kinetocardiograms taken from areas similar to conventional electrocardiograph chest leads. Records from KV_6 are not included in this analysis; however, they are almost identical in pattern to KV_5, but much smaller in amplitude and lacking some detail.

Sixty-four male subjects whose ages ranged from 20 to 30 years were studied. A careful history and a general cardiovascular examination was made on each subject. The magnitude of certain movements from each chest position was estimated by comparing the amplitude to that produced by a calibrated sine wave generator (described in more detail in the previous communication).[1]

Nomenclature

Ideally, functional nomenclature should be introduced in which the symbols used would indicate the underlying mechanism responsible for the various movements. However, some method is necessary to refer the reader to specific movements, and, as the genesis of all the waves is not known, a system has been adapted that refers to times in the cardiac cycle the waves occur, instead of to their origin. Both the peaks and the valleys of waves have been named, to avoid the confusion that is now present in the ballistocardiographic literature. (Some authors refer to the J wave as indicating the entire headward movement which follows the footward I wave, while others refer to the J wave as the headward and footward movement that occurs above a central base line.) The letters employed are the initials of the times in the cardiac cycle the movements occur, while the subnumerals refer to the various points during that period. Odd numerals have been applied to the valleys, while even numerals have been applied to the peaks. Therefore, an odd subnumber to an even subnumber (i.e., E_2–E_3) indicates an outward movement, while an even subnumber to an odd (i.e., E_1–E_2) indicates an inward movement.

Figure 1 is a drawing of KV_1 and KV_4, with all points labeled. A_1 and A_2 are points occurring during auricular systole, or between the onset of the P wave in the electrocardiogram and the onset of the Q wave.

I_1, I_2, I_3, and I_4 are points that occur during the phase of isometric contraction. Actually, this time period includes the phase of protosystole, as discussed in the previous communication, or from the onset of QRS of the electrocardiogram to the onset of carotid ejection. The sharp outward movement I_1–I_2 always occurs after the onset of the QRS complex, and is present in records obtained during heart block and auricular fibrillation, indicating that this outward movement is the result of ventricular activity and, therefore, should not be included in the auricular period. The point I_4 usually occurs before, but may occasionally be simultaneous with, the onset of carotid ejection. Therefore, this point was included with isometric contraction. As points I_3 and I_4 are not present in the right side of the chest (KV_{3R}, KV_1), I_2 is, therefore, the last point before ejection, even though I_2 on the right

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This investigation was supported by a research grant [H-959(C)] from the National Heart Institute, National Institutes of Health, U. S. Public Health Service.

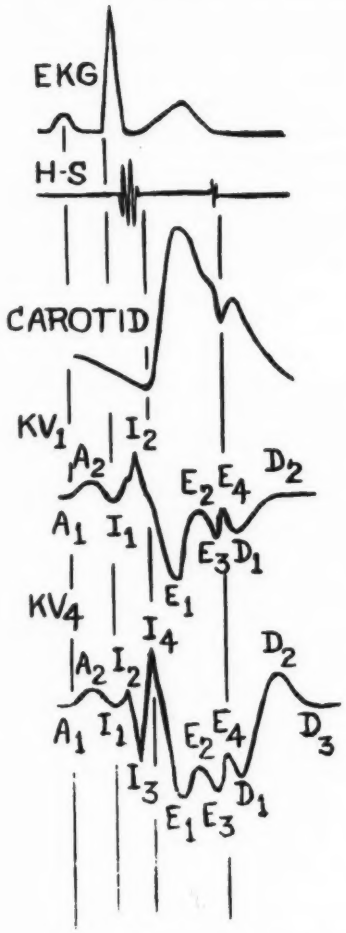

FIG. 1. The nomenclature for the kinetocardiograms is represented in a schematic drawing of records taken from KV_1 on the right side of the chest and KV_4 on the left side of the chest. The nomenclature is based upon a modified division of the cardiac cycle. All points between the onset of the P wave and the QRS complex in the electrocardiogram are assumed to be due to auricular contraction, and the latter A is used to indicate the points occurring in this period. Although the isometric contraction phase technically begins with the onset of the first heart sound and ends with the beginning of ejection, the phase of protosystole, as discussed in the preceding communication, is included in this period. The motions which begin after the onset of the QRS in the electrocardiogram are presumed to be ventricular in origin, since they occur in patients with auricular fibrillation and in complete heart block. The letter I is used to indicate this isometric contraction period. The letter E is used to indicate the period during ejection, while the movements during diastole are indicated by the letter D. Note that the odd subnumerals are all located on the valleys, while the even subnumerals are all located on the peaks of the various movements. Note also that the point I_2 in KV_1 on the right side of the chest occurs approximately at the same time as I_3 on the left side of the chest, since I_2 was the next definable point after I_1 on the right side of the chest. Thus the motion I_3-I_4 is absent on the right side of the chest.

chest occurs after I_2 on the left chest. E_1, E_2, E_3, and E_4 are used to indicate the points occurring during ejection systole, while the point E_4 may occur as late as the second heart sound; however, since it is probably the terminal point of ejection, it is labeled as part of this phase. D_1, D_2, and D_3 are used to indicate the points occurring during diastole. Diastole was not separated into isometric relaxation and rapid filling, since the waves do not lend themselves to this separation. D_1–D_2 begins in early or midisometric relaxation and often ends during rapid filling. D_3 is not a constant point, and is present only when D_1–D_2 is large; however, it occurs sufficiently often to warrant designating it by a symbol. All waves will be referred to as A_1–A_2, I_1–I_2, I_3–I_4, etc., to indicate the movement between two points.

RESULTS

It was possible to divide the patterns from the 64 subjects studied into three separate types. The divisions, initially, were made entirely on the appearance of patterns; however, on careful study there are significant differences in these groups as to amplitude and distribution of certain movements. Thus it now appears that there are definite criteria for the divisions as described, which, in addition, may be of physiologic importance.

Type I

Configuration. The most common pattern found was designated as type I, and occurred in 50 of the 64 subjects, or in 78 per cent, and resembles the general pattern described in the first communication.[1] All of the details will not be repeated here, but certain important features should be emphasized. Figure 2 is a labeled record of KV_{3R} and KV_4 in type I pattern. Approximately 0.02 second after the onset of the QRS complex, there begins an outward movement (I_1–I_2), most pronounced in KV_{3R} and KV_1; however, it may appear as far leftward as in KV_4. A sharp inward movement occurs in KV_4 (I_2–I_3), and sometimes is noted

as far rightward as KV_2. This inward motion (I_1–I_2) is then followed by a prominent outward movement (I_3–I_4) in KV_4, corresponding clinically to the apical thrust. This outward motion (I_3–I_4) begins 0.02 second to 0.05 second before the onset of carotid ejection, and is 0.06 to 0.11 second after the beginning of the QRS in the electrocardiogram, with an average of 0.08 second. The movement (I_3–I_4) is most pronounced over the apex but is present to a lesser degree often as far rightward as KV_2, but never in KV_1. Simultaneously with the I_3–I_4 in KV_4, or very shortly after it, the right chest (KV_{3R} and KV_1) begins moving inward (I_2–E_1). It is important to point out that the beginning of this inward motion (I_2–E_1) of the right chest begins as much as 0.06 second before the carotid upstroke, and is, therefore, not primarily related to the ejection process. Figure 3*A* is a drawing of the relationships of KV_1 to KV_4 during protosystole and isometric contraction in type I subjects.

Amplitude. The amplitude of the principal movements were measured. Table 1 includes the mean of the amplitudes, range, and standard deviations computed for 36 type I subjects. (Data from 14 subjects were not included, since records were obtained before the calibration procedure was being employed.) The range and standard deviations are wide, indicating a marked variability in amplitude among the normal subjects.

In general, the individuals with thick chests had smaller amplitudes. The outward movement during isometric systole, which correlated with the apical thrust (I_3–I_4), has the greatest amplitude in KV_4 position, averaging 25 microns. Since similar small outward movements were noted in KV_2, KV_3, and KV_5, the force producing the apex thrust is not localized only at the area of the point of maximum impulse, but moves the adjacent areas outward to a lesser degree. (This is consistent with what was found on cadaver experiments.[1]) The magnitude of the apical thrust was greatest in subjects with palpable apex beats, although no attempt was made to apply the bellows to the exact spot of the apical thrust. Figures 4*A* and *B* illustrate a record obtained from a subject with an easily palpable apex beat, and a subject with no palpable beat. The outward movement (E_1–E_2) during ejection systole,

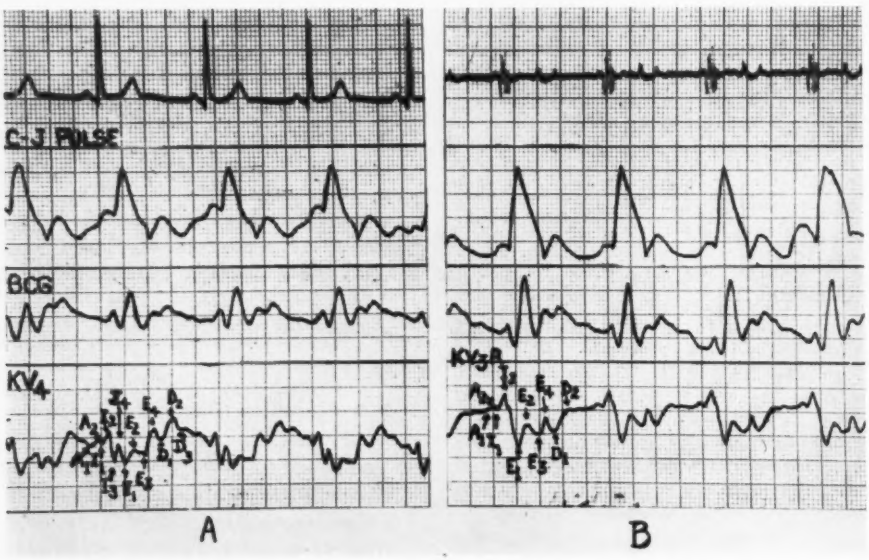

FIG. 2. *A* and *B* are records obtained in the KV_4 and KV_3R positions, with the various points in one complex labeled. Note that KV_3R resembles KV_1 in the general configuration. Both of these records were from the same type I subject.

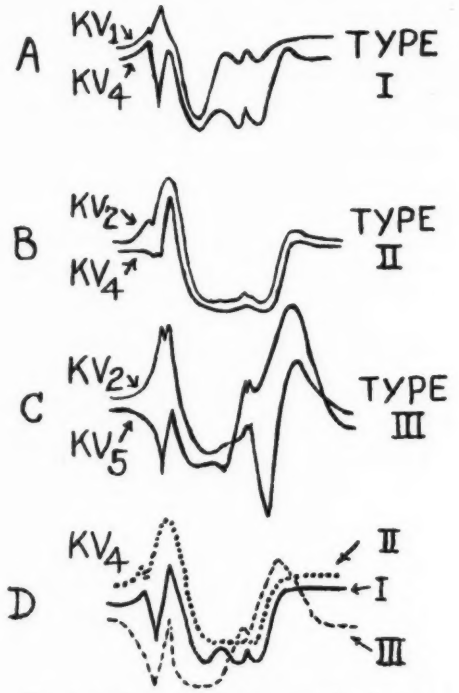

FIG. 3. *A*, *B*, *C*, and *D* are composite diagrams of the features in the various types. (*A*) A diagram of the pattern obtained from the KV_1 position and KV_4 position in type I subjects. Note the marked inward movement during isometric contraction (I_2-I_3) is present in KV_4, during which time the record in KV_1 continues to go outward. (*B*) A diagram of KV_2 and from KV_4 in a type II subject superimposed. Note the apparent absence in KV_4 of the I_2-I_3 movement with apparent fusion of I_1-I_2 with I_3-I_4 in KV_2 resulting in a slow general outward motion occurring during isometric contraction. This characteristic is apparently not an artifact, since all type II records were repeated a week later and found to be identical to the original pattern. The movements during the isometric period of diastole tend to be small in amplitude. The record in the KV_1 position is not too different from KV_1 noted in other type I subjects. (*C*) A composite diagram of KV_2 and KV_5 from a type III subject. Note that in KV_2 the outward movement I_1-I_2 is prominent, being absent in the KV_4 position. The E_4-D_1 movement, or the inward movement which occurs in early isometric relaxation, is most pronounced in KV_2 and very small in KV_5, while the converse is true for the E_3-E_4 movement, occurring in late systole. Note the large diastolic movements in both KV_2 and KV_5 records in type III. (*D*) Represents superimposed records from type I, type II, and type III from the KV_4 position. Note that type I records which occur in the majority of subjects, or 78 per cent, apparently appears to be a mixture of both type II and type III records.

which parallels the IJK waves of the ballistocardiogram, is most marked in the KV_1 area and much smaller over the left precordium.

Occasionally, a subject will have one movement which is exaggerated in amplitude. Eight subjects with type I pattern were noted to have

TABLE 1.—*The Mean Amplitudes, Range of Values in Microns, and Standard Deviations of the Various Movements in Type I Subjects*

	No. of Obs.	I_3-I_4	I_4-E_1	E_1-E_2	E_2-E_4	E_4-D_1	D_1-D_2
KV_1	36						
Mean		0	75	37	19	19	28
Range		0	27–154	0–102	0–43	0–55	0–64
σ			34	26	12	15	21
KV_2	36						
Mean		8	65	15	19	18	48
Range		0–30	11–204	0–102	0–49	0–43	0–204
σ		8	36	18	10	12	39
KV_3	35						
Mean		20	51	10	22	18	49
Range		0–54	18–106	0–30	0–75	0–57	0–120
σ		12	26	13	12	12	28
KV_4	36						
Mean		25	39	7	15	11	33
Range		7–92	0–142	0–31	0–61	0–42	0–138
σ		19	31	8	11	8	27
KV_5	35						
Mean		8	19	6	7	5	18
Range		0–27	0–151	0–34	0–24	0–19	0–68
σ		6	25	8	6	5	14
KV_5R	26						
Mean		0	52	33	12	14	18
Range		0	12–104	0–84	0–30	0–48	0–71
σ			24	20	7	11	18

a very prominent outward movement (D_1–D_2), beginning in isometric relaxation and paralleling the MN upstroke of the displacement ballistocardiogram. This movement (D_1–D_2) may be much greater than the movements associated with the systolic portion of the cardiac cycle. Figure 5 is a record from a subject in which this movement (D_1–D_2) was

especially prominent. The movement (D_1–D_2) could not only be felt clinically but, on inspection, it was noted that the entire left chest moved outward. The force producing this movement (D_1–D_2) apparently is greatest in magnitude in KV_2; however, it it not as localized as the apex thrust, being distributed over the entire left anterior chest (table 1). A diastolic thrust has been previously described to be associated with pericardial scarring, if associated with systolic retraction of the sternum, absence of apical impulse, and sudden emptying of the cervicle veins.[2] No pathologic causes for this large outward movement (D_1–D_2) in isometric diastole could be found in any of these eight subjects. It is possible that the last part of this movement is augmented somewhat by the filling of the heart.

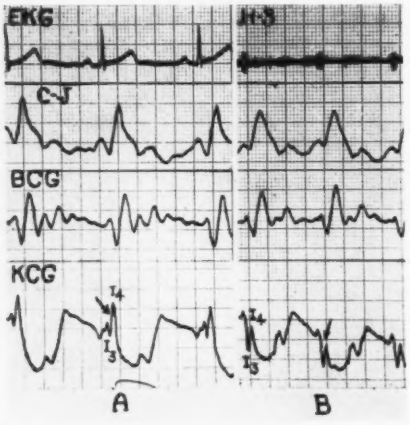

FIG. 4. *A* is a kinetocardiogram obtained from the KV_4 position in a subject with an easily palpable apex thrust. Note the marked outward movement I_3-I_4. *B* illustrates the record obtained from the KV_4 position in a subject who had no palpable apex thrust; note the same movement (I_3-I_4) is present but is below the diastolic base line and, therefore, would not be expected to be palpable.

Type II

Configuration. Type II patterns occurred in nine (14 per cent) of the subjects studied. The chief variations from type I are noted during the period of isometric contraction. Figure 6*B* is a record from a subject with type II pattern, with the other two types included for contrast. In these subjects, the most significant feature is the apparent absence of the sharp inward movement (I_2–I_3) which occurred at the time of the first heart sound in type I subjects. The initial outward movement (I_1–I_2) that begins shortly after the onset of the QRS of the electrocardiogram is apparently fused with the outward movement (I_3–I_4) of the apical thrust. Often notchings are noted where the two outward forces are superimposed; the notch occurring at the usual time when the movement of the apical thrust begins. Occasionally, subjects will have the outward apical thrust motion (I_3–I_4) in KV_4 occurring at the same time as in type I, but still lack the preceding inward motion. Figure 3*B* is a schematic drawing of KV_2 and KV_4 superimposed to show these relationships. Thus there occurs a well-marked outward movement (I_1–I_4) during protodiastole and isometric contraction, going above the diastolic baseline, and followed by a slow inward movement (I_4–E_1) with ejection. Records from KV_1 in type II are similar to those obtained in KV_1 of type I, while records from KV_2 and KV_3 do not have the transition-like quality noted in type I, but resemble KV_4 in pattern and in magnitude (fig. 7 and table 2).

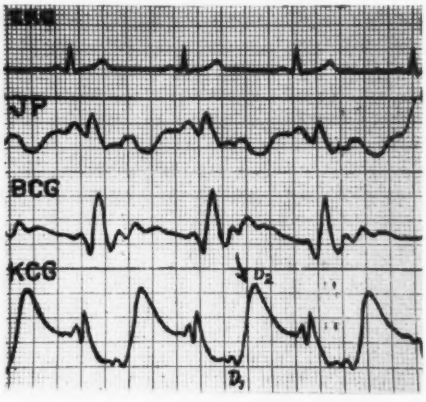

FIG. 5. A record obtained from an individual in which the diastolic movement (D_1-D_2) is prominent. The arrow points to the movement. In this subject a diastolic outward motion could be detected clinically over the anterior chest by both palpation and inspection. An exaggeration of this movement occurred in approximately eight of the type I subjects. Apparently the exaggeration of this movement is only a physiologic variation in the normal type pattern.

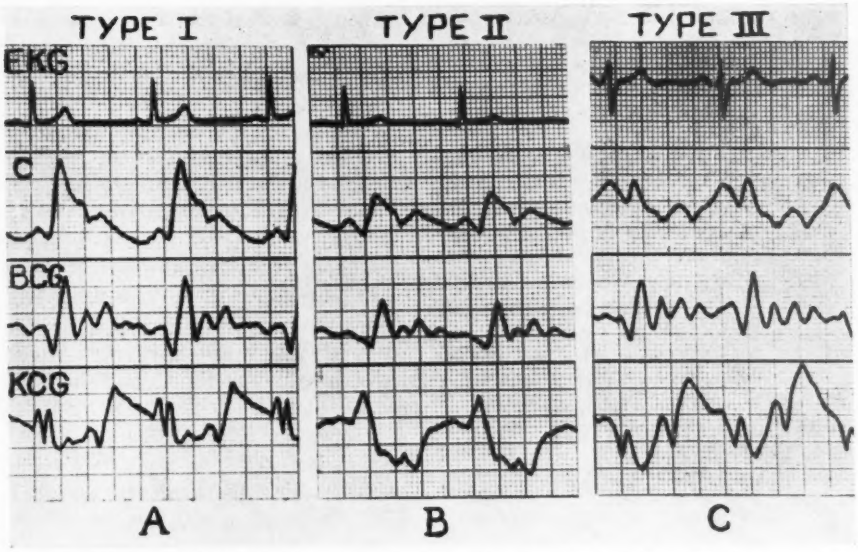

FIG. 6. (*A*) A record obtained in a type I subject from the KV_4 position. (*B*) An example of a record from the KV_4 position in a type II subject. Note the apparent absence of the sharp inward movement in type II records which occurs during isometric contraction; instead, there is a slow outward movement preceding ejection. The movements occurring during diastole also tend to be small in type II subjects. The ballistocardiogram in this subject has an apparent absence or an inverted GH upstroke. (*C*) A record obtained from the KV_4 position of a type III subject. Note the prominent diastolic movements which occur in type III subjects. The diastolic portion of the ballistocardiogram are also especially prominent in these individuals; however, some subjects in type I also have equally prominent diastolic movements.

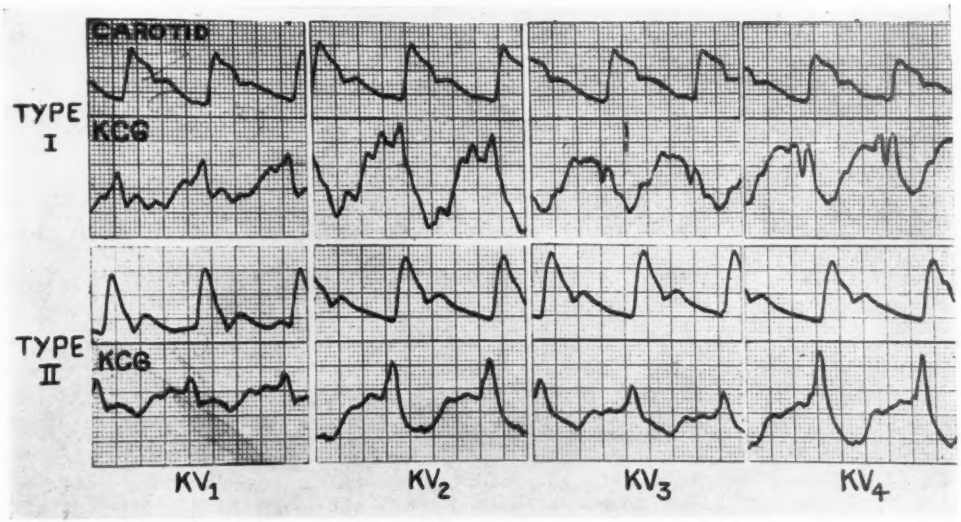

FIG. 7. Records from the KV_1, KV_2, KV_3, and KV_4 positions from both type I and type II individuals. Note that in type I subjects there is a transition from KV_1 to KV_4, while in type II the same type pattern is noted over the entire anterior precordium. The records KV_1 and KV_3 in the type II illustrations appear smaller in amplitude than KV_2 and KV_4 records because of difference in sensitivity setting of the recording galvanometer.

TABLE 2.—*The Mean Amplitudes, Range of Values in Microns, and Standard Deviations of the Various Movements in Type II Subjects*

	No. of Obs.	I_3–I_4	I_4–E_1	E_1–E_2	E_3–E_4	E_4–D_1	D_1–D_2
KV_1	9						
Mean		11	46	17	9	16	25
Range		0–25	22–61	0–34	0–30	4–35	10–36
σ		13	19	12	9	11	9
KV_2	9						
Mean		34	78	4	10	14	57
Range		0–77	30–154	0–26	0–38	0–30	12–101
σ		26	41	9	13	11	8
KV_3	9						
Mean		36	72	2	12	17	47
Range		2–60	18–128	0–17	0–38	3–27	15–89
σ		13	30	6	14	10	8
KV_4	9						
Mean		32	56	2	12	9	35
Range		4–68	20–101	0–14	0–34	0–14	8–54
σ		21	28	4	13	6	16
KV_5	9						
Mean		12	17	0	4	3	18
Range		0–34	12–34		0–12	0–9	10–51
σ		8	8		5	4	14

Although type II has a well-defined outward movement occurring in protodiastolic isometric contraction, none of these subjects had a palpable apex thrust. This is possibly explained by the fact that the outward movement is over the entire precordium, and not localized in one area, as is the outward movement (I_3–I_4) in type I. Although there is no apical thrust, per se, the observer may note an outward movement of the entire precordium. The outward movement (E_3–E_4) was small in all type II subjects, as was the following inward movement (E_4–D_1). Frequently, only a small notching occurred at this time. However, the outward movement (D_1–D_2), which parallels the MN upstroke in the ballistocardiogram, was prominent.

Of the nine type II subjects, one gave a past history compatible with rheumatic fever at the age of 6; however, he has had no recurrences, nor is there any detectable heart damage present at this time. There were no murmurs present in any of the subjects. Seven subjects had thin chests, while two subjects had thick chests and were much heavier in stature. All nine subjects in type II had electrocardiograms with a vertical QRS axis; however, some subjects in type I also had a vertical QRS axis. The precordial electrocardiographic leads, in general, had a prominent R in V_1, V_2, and V_3,

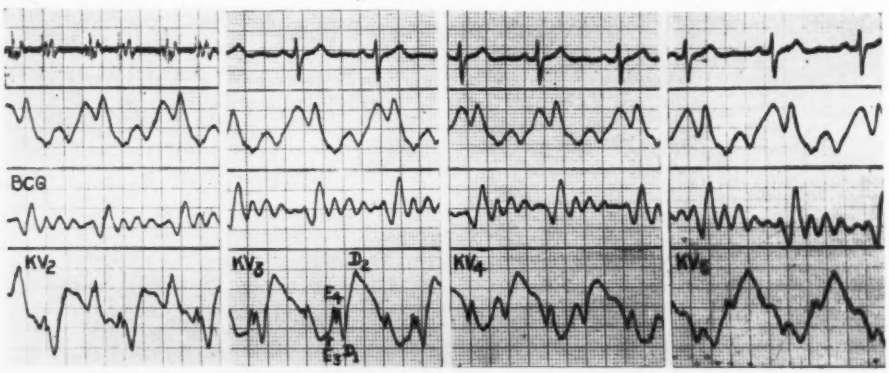

FIG. 8. Records from the KV_2, KV_3, KV_4, and KV_5 positions from a type III subject. Note the extremely prominent diastolic movements. The early outward movement in isometric systole I_1–I_2 is extremely prominent in the KV_2 position, and almost absent in the KV_5 position. The outward movement (E_3–E_4) late in systole is most prominent in the KV_4 and KV_5 positions, while (E_4–D_1), the early isometric relaxation inward movement, is most prominent in KV_1 and KV_2 positions.

and sometimes showed transitions of the QRS in V_4. In addition to the alteration in the pattern during isometric systole in type II subjects, the displacement ballistocardiograms had absent or, at most, very small GH upstrokes (fig. 6*B*).

Amplitude. The total outward movement during isometric contraction (I_1–I_4) was of equal amplitude in KV_2, KV_3, and KV_4 (table 2). The difference in amplitude of this outward movement in type I and type II records was significant. The occurrence of an outward movement (I_1–I_4) during this time in KV_1 is important to note.

Thus the force producing the outward movement of the apical thrust apparently is fused with the outward movement, beginning shortly after the onset of the QRS complex. This force is apparently distributed equally to KV_2 and KV_4 positions, since the amplitudes are similar (table 2).

Type III

Configuration. Five subjects, or 8 per cent, were found to have type III patterns, Figures 6*C* and 8 illustrate the pattern in type III subjects. The movements in type III subjects varied both during the isometric contraction and relaxation phases of the cardiac cycle. The initial outward movement (I_1–I_2) occurring shortly after the onset of the QRS complex was especially pronounced in KV_{3R}, KV_1, and KV_2, being absent in KV_4 and KV_5. In one subject the magnitude and sharpness was of such a degree as to produce an easily palpable and visible thrust only 2 cm. from the left parasternal line in the fourth intercostal space. The inward movement (I_2–I_3) at the end of the first heart sound is much deeper in KV_4 and KV_5 than in type I, and appears to begin with or shortly after the onset of the outward movement noted in KV_1 and KV_2.

The outward movement (E_3–E_4), that usually occurs just preceding the carotid incisura, begins earlier, and in one subject began shortly after the inward movement (I_4–E_1). E_3–E_4 is significantly increased in amplitude in KV_4 and KV_5, but small in KV_1 and KV_2. Conversely, the inward movement (E_4–D_1) that begins with the carotid incisura is large in amplitude in KV_1 and KV_2, being small in KV_4 and KV_5. The outward movement (D_1–D_2) that begins in isometric relaxation is pronounced from the entire precordium. Figure 3*C* illustrates KV_5 superimposed on KV_2.

TABLE 3.—*The Mean Amplitudes, Range of Values in Microns, and Standard Deviations of the Various Movements in Type III Subjects*

	No. of Obs.	I_3–I_4	I_4–E_1	E_1–E_2	E_3–E_4	E_4–D_1	D_1–D_2
KV_1	4						
Mean		0	99	44	19	34	63
Range			42–131	24–61	6–34	12–54	12–85
σ			41	20	12	21	35
KV_2	4						
Mean		26	95	17	15	26	96
Range		0–69	60–135	0–51	0–25	24–48	64–135
σ		30	25	24	11	13	29
KV_3	4						
Mean		22	54	16	25	30	73
Range		0–31	43–82	0–34	12–36	18–36	42–82
σ		14	19	14	11	10	19
KV_4	4						
Mean		23	47	4	35	14	58
Range		8–41	6–86	0–15	13–61	0–24	15–102
σ		14	33	8	17	11	35
KV_5	4						
Mean		32	32	3	36	10	37
Range		9–72	15–71	0–10	32–41	6–17	22–71
σ		29	26	5	4	5	30
KV_2R	3						
Mean		0	68	59	13	26	47
Range		0	32–85	16–66	0–25	16–43	24–69
σ			31	13	13	15	23

An S_1, S_2, S_3 pattern was noted on the electrocardiogram in all type III subjects; however, a few subjects in other groups had similar electrocardiograph patterns. The displacement ballistocardiogram in type III subjects revealed especially prominent K,L,M,N

sequences (fig. 6*C*); however, occasionally these waves are just as marked in some subjects in type I as in figure 6*A*.

Amplitude. Table 3 contains the amplitudes of the various movements for four of the five subjects. The amplitude of the three principal movements during the relaxation period was greater than the corresponding movements in type I, and was found to be of significant difference when compared mathematically, adding evidence that type III is a true physiologic variant.

Thus type II apparently is formed by an absence of the early isometric contraction inward movement with a fusion of the apical thrust with the early outward movement (I_1–I_2) while type III has an exaggerated early outward movement (I_1–I_2) in KV_2 with an equally prominent inward movement in KV_4 and KV_5. Type I appears to be a mixture of the two opposite variations. Figure 3*D* has the three types superimposed to illustrate the significant features of each.

Comment

The full understanding of the differences between types I, II, and III would require a knowledge of the cause of the various waves, as well as physiologic and anatomic variations not yet available. At the present time, there is no apparent explanation for the variations noted, and a discussion will have to be delayed until a much greater understanding of the records is attained. An hypothesis of the genesis of the various waves will be presented in a subsequent communication. However, it

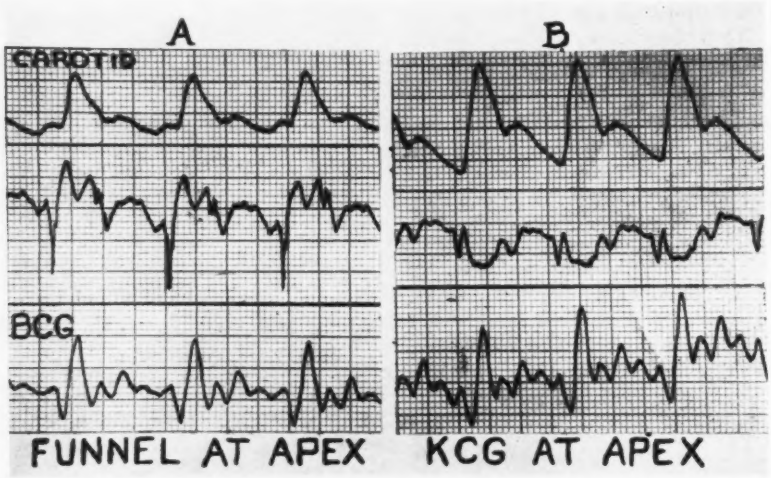

Fig. 9. (*A*) An apex cardiogram obtained by placing a 2 inch funnel connected to a piezoelectric transducer over the apex of the heart. Note that there occurs a marked outward movement during isometric systole (probably the thrust of the apex), which remains above the base line during the greater part of systole, and returns only during early isometric relaxation. This record resembles previously published apex cardiograms. (*B*) A record obtained with the bellows from the apex of the same individual. The amplitudes of this record are different from *A* primarily because of the difference in degree of sensitivity of the recording galvanometer. Note that an outward movement occurs at the same time of the apical thrust, as in the apex cardiogram; however, it is followed immediately by a well-marked inward movement during systole. The diastolic movements are also more clearly demarcated in the kinetocardiogram than those of the apex cardiogram. The kinetocardiogram records the absolute movement of the chest wall, while the apex cardiograms record relative movements of the chest wall and tend to vary according to the diameter of the pick-up device employed. The kinetocardiograms are reproducible and constant in the same individual and, as has been pointed out, approximately 78 per cent of subjects have the same general type pattern from comparable positions over the anterior chest wall.

is important at the present time to point out several differences between the records recorded with the bellows and those obtained by other technics.

Comparison of the Kinetocardiogram with the Apex Cardiogram and Other Low-frequency Precordial Records

Often the kinetocardiograms obtained from KV_4 position resemble the apex cardiograms previously published.[2-5] However, instead of the three normal types as were noted in this study, only two different forms of records have been noted previously.[5] One type was somewhat like type I, while the other was different, in that the record goes outward early with the apical thrust and remains out during all of systole. We have never noted this latter type in normal subjects, with the technics being employed. The chief reason for the variations lies in the fact that the kinetocardiograms are recorded from a fixed point above the chest wall, while the other methods record the relative motion between two points. Any device resting primarily on the chest wall will not record, or will minimize the movement that the entire chest or part of the chest makes, and registers only the relative movements. Thus the recorded motion between the two points on the chest wall will depend on the distance between the points. (If a microphone type of pickup is used against the chest wall, the outside rim will be the limiting point, and the movement of the area included will be the factor determining the type of record.) The records of Johnson and Overy[4] differ from those obtained by Luisada and Magri,[5] possibly since the funnel type of endpiece used by Johnson was smaller in diameter than the end of the microphone employed by Luisada. Figure 9 contains a record obtained with a 2 inch funnel at the apex, and a record obtained with the bellows pickup for the KV_4 position. Note the change in detail of that obtained with the funnel, from the kinetocardiogram, which in this instance resembles the conventional apex cardiograms. In the kinetocardiogram, the anterior chest begins inward shortly after the outward movement of the apex thrust, resulting in the inward movement during ejection (I_4–E_1). This is absent in the apex cardiograms. Thus the present method permits the recording of the absolute movement of a specific small point (7 mm. in diameter) on any place over the chest wall. The magnitudes can be easily estimated and the procedure calibrated,[1] and all records are reproducible and constant.

Comparison of Records with the Pneumocardiograms

Records from KV_{3R} positions, and frequently from KV_1 (fig. 2), resemble the pneumocardiograms previously published by others.[6, 7] Pneumocardiograms have been taken simultaneously with kinetocardiograms and found to differ primarily in time relationships. The inward motion I_2–E_1 in the KV_{3R} records occurred 0.08 second before the inward movement of the pneumocardiogram. Thus it seems that such a lag would be unlikely if the two records were due to the same events in the chest. Recently, Hamilton and Lombard presented evidence that changes in interthoracic pressure were negligible in producing the pneumocardiograms.[6] The onset of the inward motion noted in KV_{3R} and KV_1 precedes ejection too far to indicate that it is related to the pressure changes during ejection. It is possible, however, that although the onset is not related to ejection or to the changes in interthoracic blood volume, the continuation and depth of inward movement is related to these factors. Thus the records obtained from KV_{3R} and KV_1 are probably not related to pneumocardiograms because of the marked time difference between the two records. Kinetocardiograms from the left precordium are too markedly different from the pneumocardiograms to indicate any primary relationship, and are probably more related to the shape changes, positional movement, and impacts of the heart.

Conclusions

1. Kinetocardiograms and correlating physiological events were obtained on 64 young normal male subjects.

2. A nomenclature has been submitted that is based upon the division of the cardiac cycle.

3. Three types of variations in the precardial movements were noted.

4. Type I occurred in 78 per cent of the subjects and appeared to be a mixture of type II and type III records.

5. Type II occurred in 14 per cent of the subjects and consisted of a prominent outward movement over the entire left precordium, beginning shortly after the onset of the QRS in the electrocardiogram and then moving inward with ejection. The movements during early diastole were small.

6. Type III occurred in 8 per cent of the subjects studied and consisted of an absence of the early outward movement during isometric contraction (I_1–I_2) in the KV_4 position with a sharp inward movement I_2–I_3. All diastolic movements are enlarged in type III subjects.

7. Certain differences have been pointed out between the records reported (KCG) and apex cardiograms obtained by other technics and pneumocardiograms.

Sumario Español

Se presenta un análisis de los patrones y amplitudes de los movimientos precordiales. Sujetos adultos jóvenes normales mostraron tres tipos de patrones. Tipo I ocurrió en 78 por ciento, tipo II en 14 por ciento y tipo III en 8 por ciento de los sujetos estudiados. Las variaciones del kinetocardiograma del cardiograma del ápice y del pneumocardiograma se discuten.

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Studies of Quantitative Ballistocardiography

The Velocity of Body Displacement in Patients with Heart Disease

By Vincenzo Masini, M.D., and Paolo Rossi, M.D.

The speed of body displacement was calculated on 70 per cent of the ballistocardiograms recorded in 128 patients suffering from heart disease. Results show that the values are generally lower in cardiac patients than in normal subjects, with the exception of cases with high stroke volume. The diminution of the speed of body displacement is proportional to the severity of ballistic abnormalities and to the functional state of the heart. A tentative explanation of the findings is presented.

IN a preceding paper[1] we suggested th the velocity of body displacement (Vb) be used as an index of quantitative ballistocardiography, inasmuch as the calculations of cardiac output and maximal cardiac force, according to Starr,[2] are methods open to criticism on both theoretic and practical grounds.[3]

According to our experience, the velocity of body displacement is a useful and practical index for the following reasons: (1) It is a direct expression of the ballistic forces which develop during the ejection phase of the ventricular systole, and thus it gives an indirect estimate of the work and strength of the heart. (2) The values obtained are uniform and independent of body weight and surface area. (3) The calculation is simple. (4) The value may be calculated not only on normal tracings but also on tracings which are abnormal in form.

The value of the velocity of body displacement is obtained by dividing the vertical distance between the tips of the I and J waves, expressed in millimeters, by the time in seconds between the same points (fig. 1). In our study of 100 normal subjects, we found that the mean value was 68 with a standard deviation about the mean of 14 mm. per second. This value is higher in the male (76 with a standard deviation about the mean of 17.5 mm. per second) than in the female (59 with a standard deviation about the mean of 11 mm. per second).

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We have now estimated the speed of body displacement in patients suffering from heart disease, in order to study its relations with the type of heart disease, the functional state of the heart and the various ballistic patterns.

Clinical Material and Results

Our cases included 148 cardiac patients (105 men and 43 women), ranging in age from 10 to 80 years (average age 40 years). Of these, 29 had mitral and 18 aortic or combined mitral and aortic valvular disease; 23 had arteriosclerotic heart disease without hypertension; 34 had hypertensive heart disease; 17 had arteriosclerotic heart disease complicated by angina pectoris or myocardial infarction; 21 had congenital heart disease and 6 adhesive chronic pericarditis.

The congenital malformations included nine cases of tetralogy of Fallot, four of pentalogy of Fallot, one of trilogy of Fallot, one of isolated pulmonary stenosis, two of patent ductus arteriosus, and three of stenosis of the isthmus of the aorta. In three cases the type of congenital malformation was not established.

Simultaneous recording of the ballistocardiogram and the electrocardiogram was made in every case. We used a personally devised high-frequency swinging bed ballistocardiograph,[4] which was calibrated in the usual manner, a weight of 280 Gm. causing a deflection of 1 cm. The record was made with a larger amplification than usual, in order to make a more detailed study of the form and duration of the ballistic waves. The tracings

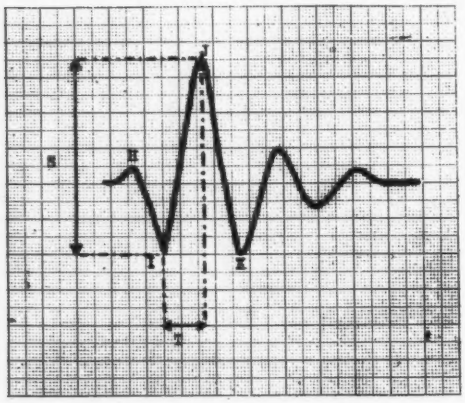

FIG. 1. Measure of the speed of body displacement. S, distance from I to J; T, time between I and J.

line because of diminished depth of the I wave which reaches the base line but does not cross below it as normally. (4) Abnormal tracings of the "early M" type. Because of the diminished I, the ballistic complex loses its common W-shaped appearance and resembles an M. This group can be further subdivided into two groups, on the basis of the large or small size of the H wave. (5) Tracings with prominent diastolic waves. The marked decrease in the amplitude of H, I and J causes K and the other diastolic waves to stand out as the dominant deflections. (6) Totally abnormal tracings. The pattern is completely irregular and indefinite and the complexes vary in form from beat to beat.

TABLE 1.—*Frequency, in Total and Per Cent Figures, of the Different Ballistic Patterns in the Different Types of Heart Disease*

Type of Heart Disease	No. of cases	Normal		Borderline		Early M		Totally Abnormal	
		No.	%	No.	%	No.	%	No.	%
Mitral valvular disease	29	14	48.3	6	20.7	3	10.4	6	20.7
Aortic valvular disease	18	8	44.4	6	33.4	1	5.5	3	16.7
Arteriosclerotic heart disease	23	7	30.4	8	10.6	5	21.6	3	13
Hypertensive heart disease	34	9	26.5	13	38.3	9	26.4	3	8.8
Coronary heart disease	17	8	47.1	2	11.7	3	17.7	4	23.5
Congenital heart disease	21	20	95.3	—	—	—	—	1	4.7
Pericarditis	6	4	66.6	—	—	1	16.7	1	16.7
Total No. of cases	148	70	47.3	35	23.7	22	14.8	21	14.2

were recorded in inspiratory apnea, expiratory apnea, and during normal respiration, but the calculations were all made on the tracings recorded in expiratory apnea, because in this position a complete absence of artifacts is more easily obtained.

We customarily classify the ballistic patterns into six groups: (1) Normal. Tracings with normal amplitude, duration and contour of the various deflections and normal relations between the various waves are included in this group. (2) Tracings which are borderline by reason of slight abnormalities in form of one or a few deflections (notching of the I-J segment, splitting of the apex of H or J, notching of K, H waves as high or higher than I waves, L waves as high or higher than J waves, etc.). (3) Tracings which are border-

For this study we have used a simplified classification, dividing the tracings into four main groups:

1. Normal. This corresponds to groups 1 and 2 of the preceding classification.

2. Borderline. Tracings showing reduced amplitude of the I wave are so classified.

3. Early M pattern.

4. Completely abnormal. This corresponds to groups 5 and 6 of the preceding classification.

Table 1 shows the frequency, in total figures and percentages, of the different abnormalities in the total number of cases and the different forms of heart disease.

On the ballistic tracings of 128 patients (that is, on all the tracings except those with a completely abnormal pattern) we have

calculated the velocity of body displacement according to the technic described in an earlier paper,[1] dividing the distance, expressed in millimeters, from I to J by the time in seconds between the same points. Results are shown in figures 2 and 3.

The functional state of the heart was known in 121 cases. In this respect the patients were divided into two groups: group 1 includes

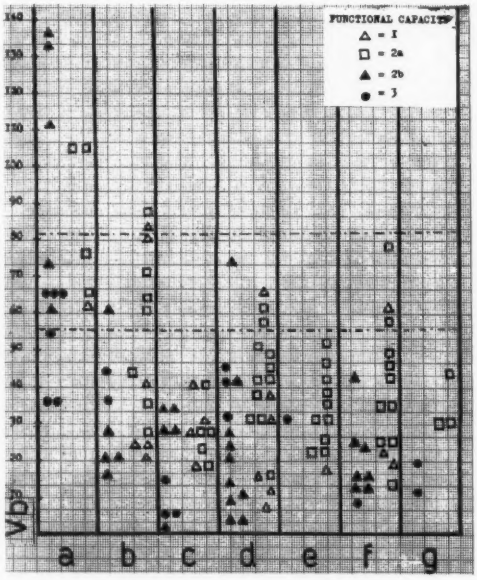

FIG. 2. Values of the speed of body displacement (Vb) according to cardiac functional capacity and the type of heart disease. *a*, aortic valvular disease; *b*, mitral valvular disease; *c*, arteriosclerotic heart disease; *d*, hypertensive heart disease; *e*, arteriosclerotic heart disease with angina pectoris or infarction; *f*, congenital heart disease; *g*, adhesive pericarditis. Broken line indicates upper limit of mean values in normal subjects.

patients classified as 1 and 2a (subjects with normal functional capacity or slight exertional dyspnea); group 2 includes the subjects classified as 2b and 3 (dyspnea even at rest or signs of congestive heart failure). The values of the velocity of body displacement according to the type of heart disease and the functional capacity of the heart are shown in figure 2. Table 2 shows the mean values for the speed of body displacement in the total number of cases, the various types of heart disease

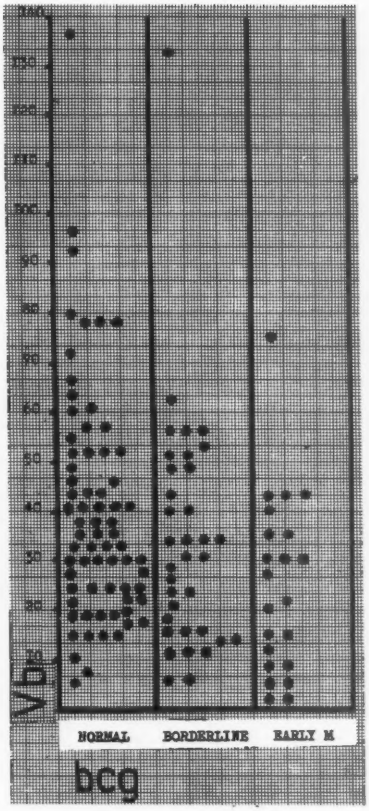

FIG. 3. Values of the speed of body displacement (Vb) in the different ballistic patterns.

TABLE 2.—*Mean Values of the Velocity of Body Displacement in the Total Number of Cases, the Various Types of Heart Disease and in the Different Grades of Cardiac Functional Capacity*

Type of Heart Disease	No. of Cases	Functional Capacity		Total
		Grades 1 & 2a	Grades 2b & 3	
Aortic valvular disease	16	87	75.6	79.2
Mitral valvular disease	20	50.8	31.4	44
Arteriosclerotic heart disease	17	29	19	24.8
Hypertensive heart disease	30	37.7	27.3	33.1
Coronary heart disease	12	32.3	30	32
Congenital heart disease	21	39.2	20.2	32.1
Pericarditis	5	35	15	27
Total no. of cases	121	42	33.3	36.2

TABLE 3.—*Mean Values of the Velocity of Body Displacement in the Different Ballistic Patterns*

Ballistocardiogram	No. of Cases	Mean Value of Vb
Normal	70	41.7
Borderline	35	35.2
Early M	22	26.3
Total	127	36.7

tients; that is, on all the ballistocardiograms in which the I-J interval can be identified with certainty. This proves the practical value of this index which, in this respect, is of greater value than the calculation of stroke volume inasmuch as the latter can only be computed on tracings normal in form.

2. The figures for the velocity of body displacement are usually lower in cardiac patients

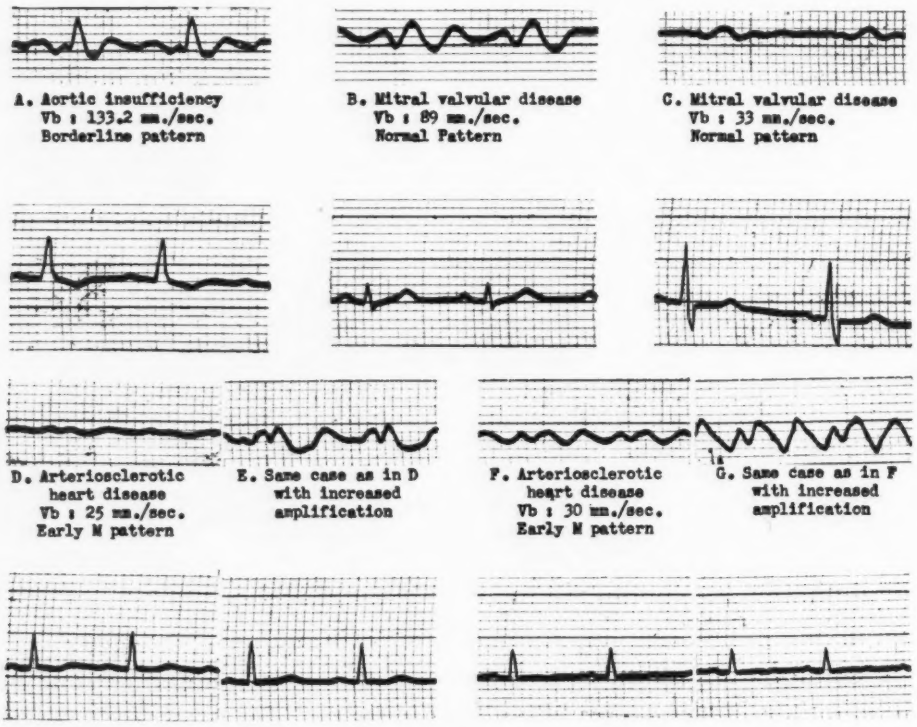

FIG. 4. Some examples of the speed of body displacement (Vb).

and in the different grades of cardiac functional capacity.

The relation between the values of the speed of body displacement and the form of the ballistocardiogram is shown in figure 3 (single values) and table 3 (mean values).

COMMENT

The following conclusions may be drawn from our study:

1. The speed of body displacement can be calculated in a large percentage of heart patients than in normal individuals: consequently the mean value obtained in our patients was lower than the mean value of normal subjects. Exceptions to this rule are found in patients with aortic insufficiency or patent ductus arteriosus; the values obtained in these patients were notably higher than normal.

3. The velocity of body displacement varies according to the functional capacity of the heart, being lower in patients with heart failure. This conclusion is confirmed by the higher mean values found in patients with

good functional capacity, regardless of the particular type of heart disease, as compared with the mean values obtained in patients with impaired functional capacity.

4. A comparison between the velocity of body displacement and the form of the ballistocardiogram has shown that the speed of body displacement diminishes as I becomes smaller, so that the mean value of normal tracings is higher than that of borderline tracings, and the last in turn is higher than the value of tracings of the early M type. It should be noted, however, that this is only a general rule, inasmuch as very low values of the velocity of body displacement may be observed not infrequently even in the presence of tracings normal in form.

It is difficult to give an exact interpretation of the results, because we do not yet know all the elements which determine the amplitude of the ballistocardiogram.

It was thought at first that there was a direct relationship between the amplitude of the ballistocardiogram and the value of the stroke volume, because the size of the ballistocardiogram increases with exercise and in many physiologic and pathologic conditions that cause an increase in the stroke volume. Recent studies on the action of nitrites have shown that an increase in the amplitude of the ballistocardiogram can occur without a concurrent increase in the stroke volume.[5]

Starr[2, 6] also has demonstrated experimentally that, the stroke volume being equal, the amplitude of the ballistic tracing is related both to the amplitude of the force of the heart and to the way this force is applied during the ventricular ejection.

It is our opinion that the changes in the amplitude of the ballistocardiogram may be due both to variations in the stroke volume and changes in the speed of ejection. It should in fact be noted that the law of the conservation of momentum cannot be rigidly applied to the ballistic system of the body, because the impact of the blood upon the aortic arch and the pulmonary vessels generates other forces acting in the opposite direction. However, it seems obvious that the quantity of motion imparted to the body should be roughly proportional to the quantity of motion imparted to the blood, and as the latter is determined by multiplying mass by velocity, we believe that variations in the size of the ballistocardiogram may be due to either one or the other or both of these factors. Therefore we can interpret the diminished speed of body displacement in patients with heart disease as being the result of diminished stroke volume, and/or diminished ejection speed; according to Starr, the latter may be caused by changes in the amplitude of the force of the heart or in the way the force is applied.

This would also explain why the decrease in the velocity of body displacement is proportional to the degree of heart impairment.

The increased speed of body displacement which has been noted in some forms of heart disease (aortic insufficiency, patent ductus arteriosus) is probably related to increased stroke volume.

Generally the decrease in the speed of body displacement is more evident in tracings abnormal in form. Inasmuch as, according to Starr's experiments, the morphologic changes are caused by abnormalities in the contour of the ventricular ejection curve, one must admit that in these cases, in addition to a low stroke volume and/or diminished speed of the blood, there is also an abnormal ventricular ejection.

It is difficult to understand clearly why in some forms of heart disease the velocity of body displacement is diminished, in spite of the absence of graphic abnormalities. According to our experience, this finding is confined almost exclusively to mitral stenosis with moderately good functional capacity. This leads to the hypothesis that in these cases the diminished speed of body displacement is related to the low stroke output, due to purely mechanical factors, whereas the speed and contour of the ventricular ejection curve are still normal owing to the good functional condition of the heart muscle.

Conclusions

The following conclusions may be drawn from our study:

1. The velocity of body displacement (Vb)

may be estimated on over 70 per cent of the ballistocardiograms recorded in patients suffering from heart disease.

2. The value of the speed of body displacement is usually lower in cardiac patients than in normal subjects.

3. However, in patients having heart disease with a high stroke output, and especially in aortic regurgitation, the values of the velocity of body displacement are higher than normal.

4. There is a direct relationship between the values of the velocity of body displacement and the functional state of the heart.

5. As a general rule, the values of the velocity of body displacement diminish as the graphic abnormalities become more pronounced. However, a marked decrease of the speed of body displacement may be found not infrequently when the ballistocardiogram is still normal in form. It is suggested that the diminished velocity of body displacement observed in these cases may be due to a diminished stroke output, independent of hemodynamic changes in the ventricular ejection.

The results of our study confirm that the calculation of the speed of body displacement is a valuable index of quantitative ballistocardiography. In addition they provide confirmatory evidence for the theoretic assumption that the velocity of body displacement is a reliable quantitative expression of the complex hemodynamics of the ejection phase of the ventricular systole.

Summary

The velocity of body displacement (Vb) has been calculated on 128 ballistocardiograms recorded in 128 patients suffering from heart disease. The relations of the values of the speed of body displacement, to the type of heart disease, the functional state of the heart and the different ballistic patterns have been studied.

The following conclusions are presented:

1. The velocity of body displacement may be estimated on over 70 per cent of the ballistic tracings recorded in cardiac patients.

2. The figures for the velocity of body displacement are usually lower in cardiac patients than in normal subjects. However, in heart disease with high stroke output and especially in aortic regurgitation, the values are higher than normal.

3. As a general rule, the values of the velocity of body displacement diminish as the ballistic abnormalities become more pronounced. However, a marked decrease of these values may be found not infrequently when the ballistocardiogram is still normal in form. A tentative explanation of this finding is presented.

Acknowledgment

The authors wish to express their appreciation and gratitude to Dr. Isaac Starr for his helpful suggestions and for the revision of the manuscript.

Sumario Español

La velocidad de desplazamiento del cuerpo fue calculada en 70% de los balistocardiogramas registrados en 128 pacientes con enfermedad cardíaca. Los resultados demostraron los valores generalmente mas bajos en pacientes cardíacos que en los sujetos normales, con la excepción de casos con volumen de emisión sistólica alto. La diminución en velocidad del desplazamiento del cuerpo es proporcional a la severidad de la anormalidad balística y al estado funcional del corazón. Una explicación tentativa de los hallazgos se presenta.

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The Electrocardiogram of a Beluga Whale

By Robert L. King, M.D., James L. Jenks, Jr., and Paul D. White, M.D.

In the course of our study of the comparative anatomy and physiology of the mammalian heart, it became necessary to develop a technic to obtain the electrocardiogram of the largest mammal of all. Because of its availability, the small white Beluga whale in northern waters was the first object of this research, prior to obtaining the record of a large whale, which is our ultimate aim. This article describes the process of obtaining the electrocardiogram and presents the electrocardiogram itself.

THE relationship of heart size to heart rate and to the time intervals of the electrocardiogram, in particular to the P-R interval and the QRS duration, plays an important role in the interpretation of normal and abnormal human tracings. Having become interested years ago in comparative anatomic studies of the auriculoventricular conduction systems of the hearts of the largest mammals, the whale[1] and the elephant,[2] we took electrocardiograms of several circus elephants in 1938[3] and shortly thereafter, in 1939, conceived of the possibility of obtaining such records of the whale. Our plans for this project were partly made in 1940, but they had to be abandoned temporarily because of the advent of the Second World War.

In 1952 when we were at last presented with an opportunity to take an electrocardiogram of a whale, we already possessed certain data concerning the relationship of the size of the heart to its rate and to various time intervals in normal mammals of very different sizes[4] as shown in table 1. It remained for us to discover whether or not the largest mammal of all would fit the pattern. Moreover it was necessary to develop the technic to obtain by the use of harpoon electrodes such a record in the case of the whale, an animal which had not previously been electrocardiographed; it was for that reason that we made our first attempt on a small whale, the white Beluga, in Alaskan waters. It is of this procedure that we are writing in the present paper.

This experiment was made possible by a grant from the Research Fund of the Mason Clinic, the generosity of the Sanborn Company and Dr. Paul D. White's private Research Fund.

Expedition, Method and Equipment

In the summer of 1952 we were able to arrange an expedition to obtain an electrocardiogram of a Beluga (white) whale, at Clarks Point, Bristol Bay, an arm of the Bering Sea, at the mouth of the Nushagak River. On Aug. 6, 1952, a herd of whales was easily located by a small airplane. The party was informed as to the location, to which a small cannery tender ("Monkey boat") carrying the operators and the equipment was quickly dispatched. The four operators and the electrical recording equipment were transferred to a 20-foot heavy duty skiff which was used for approaching and chasing the animal into shallow water before harpooning. This skiff was powered by two outboard motors, one of 10 horsepower and the other of 16. The head or barb of the harpoon was of native design (figs. 1*A* and 1*B*) and was made of Navy brass, loosely attached to a 7/16-inch steel rod which was fastened in the large end of a tapered wooden shaft approximately 5½ feet in length. To this barb, which became detached when imbedded in the animal, was fastened a 3/16-inch twisted nylon rope for the purpose of holding the animal to the boat. Also attached was a shielded, insulated microphone cable with a core of copper wire strands. The cable was connected to a Sanborn photographic type of electrocardiograph (Cardiette). When an attempt was made to use a direct writing electrocardiograph (Visocardiette) by converting current from 6 V to 110 V by means of a converter, so much 60 cycle interference was recorded that the tracing was not clearly legible.

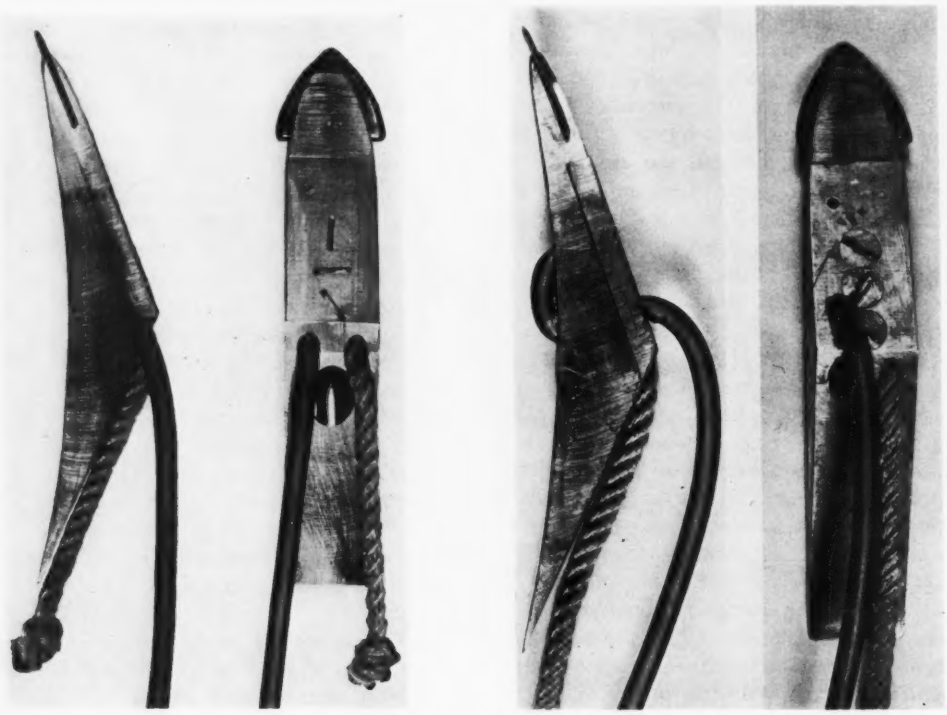
The animal was harpooned by hand ac-

cording to the method commonly employed by the natives of that area. With a single harpoon electrode imbedded in the animal's back at the approximate level of the pectoral girdle, several unsuccessful attempts were made to record an electrocardiogram. These failures were found to be due to broken connections of the cables which were insecurely fastened to the harpoon head. The barb was then modified in such a way as to fasten the cable more securely, including the wiring details, utilizing the metal shield instead of the more fragile copper core to complete the electrical connection to the galvanometer within the electrocardiograph.

The following day, after a number of varied vicissitudes of technical and mechanical nature, one of the larger male whales was singled out

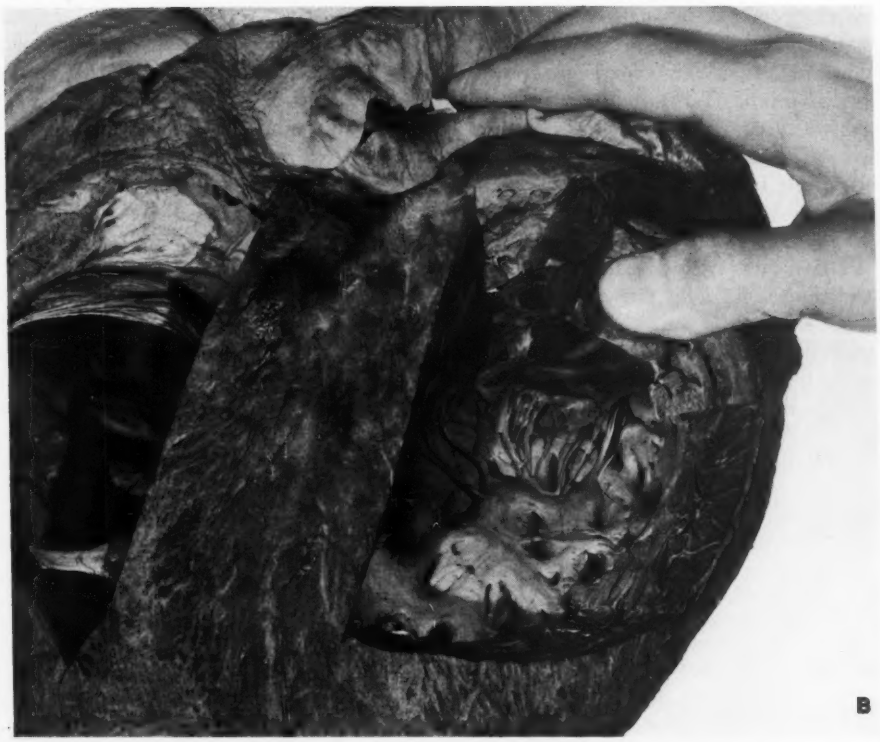
TABLE 1.—*The Relationship of Heart Size to Heart Rate and to the P-R Interval and QRS Duration of Normal Mammals*

Mammal	Heart Rate	P-R Interval	QRS Duration
Mouse	620–780	0.03–0.04 sec.	0.008–0.011 sec.
Human infant (newborn)	120–140	0.08–0.12 sec.	0.04–0.06 sec.
Human adult	50–90 (av. 72)	0.14–0.21 sec.	0.07–0.11 sec.
Elephant	24–53 (av. 35)	0.28–0.41 sec.	0.12–0.18 sec.
Beluga (small whale)	12–24 (av. 16)	?? 0.32 sec.	0.09–0.12 sec.



A *B*

FIG. 1. (*A*) Harpoon head, original design, showing cable and nylon rope attached. (*B*) Harpoon head, modified. (The actual dimensions of the harpoon head were: length, 135 mm.; width, 23 mm.; thickness, 22 mm.)



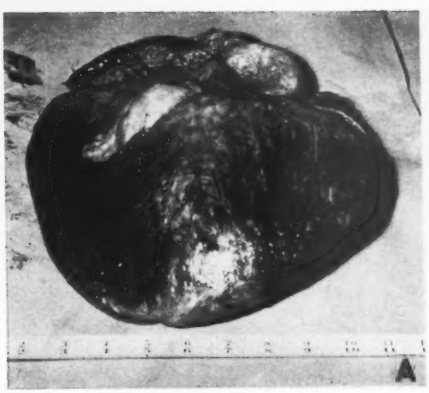


FIG. 2(*A*) (*Right*) Heart of Beluga whale, ventral aspect. (*B*) (*Above*) Heart incised to show the upper parts of the chambers of both ventricles with their respective auriculoventricular valves.

and pursued. A single ordinary harpoon head was first inserted for the purpose of holding the animal to the boat while it was alternately diving, blowing and frantically trying to escape. Then a second harpoon head, this time an electrode, was inserted into the back at the level of the pectoral girdle. This attempt was made to use a single harpoon as a unipolar electrode, with the sea water and a copper plate suspended over the side of the boat to complete the circuit. Despite electrical connections which seemed adequate, no movement of the shadow of the galvanometer beam could be detected. Therefore, a second harpoon electrode was inserted about half way down the animal's back approximately three feet from

the first electrode. With such a connection (grossly approximating lead III), definite low amplitude deflections of the galvanometer beam were observed. The standardization was increased from 1 cm. per millivolt to about 1.2 cm. per millivolt. These heartbeats were recorded intermittently over a period of approximately 30 minutes. The wounded animal was then killed by rifle fire into its head and towed to the cannery for partial dissection and utilization as food by the inhabitants of the native village.

The whale from which the electrocardiogram was made was considered to be fairly large for a Beluga. The over-all length was 14 feet. Facilities for weighing the animal were not available; however, the estimate by a number of fishermen and natives was 2500 pounds (1136 Kg.).

TABLE 2.—*Measurements of a Male Beluga Heart*

Weight of heart (fresh specimen)	2722 Gm.
Transverse diameter of heart (at base)	18.5 cm.
Right ventricular wall thickness	6 mm.
Left ventricular wall thickness	20 mm.
Circumference of right atrioventricular ring	22.5 cm.
Circumference of left atrioventricular ring	18.5 cm.
Diameter of pulmonary artery	5 cm.
Diameter of aorta	5 cm.

The heart of this animal had the general appearance and characteristics of cetaceans, being broad and flattened from top to bottom, the length being somewhat less than the width at the base. It will be noted that the apex of the heart is formed by both right and left ventricles which is true also of other marine mammals such as the porpoise. After being photographed (fig. 2*A*), the specimen was frozen for further study. Later the heart was incised to show the upper parts of the chambers of both ventricles with their respective auriculoventricular valves (fig. 2*B*).

The dissection of the hearts of male and female Beluga whales of approximately the same size, revealed structural features similar to those of other mammalian hearts. The coronary arteries and veins were similar in location, size, thickness of major branches, and distribution, to those of the human heart. The foramen ovale was closed in both specimens.

For more detailed anatomic description of the Beluga heart, the reader is referred to Watson and Young's[9] paper on this subject.

Description of the Electrocardiogram

The electrocardiogram which we obtained from this adult male Beluga whale is shown in part in figure 3. The first harpoon electrode was at about the level of the pectoral girdle near the midline, the second about the midportion of the back. These positions were considered to correspond to the left arm and the left leg respectively. Thus we believe we have utilized a lead roughly comparable to lead III. The excursion of the galvanometer was standardized so that 1 mv. was equivalent to 1.2 cm.

The chief features of the electrocardiogram were its bradycardia and the low amplitude of the complexes. Due to somatic interference, many of the complexes are so distorted as to render them unsuitable for measurement. At times the record was quite steady, evidently when the whale was less active; at other times there was much gross movement of the tracing doubtless due to much more bodily activity, but the heartbeats were always evident. The rate varied from 12 per minute or a little less up to 24; much of the time during the long tracing taken it was 16 or 17.

The P waves are very poorly defined throughout the entire record, which may be due to the fact that this lead was dorsal in position, a long way from the heart and with the electrodes not very far apart. Many beats showed no evidence of any P waves at all but here and there are to be seen very small inverted movements of the tracing about 0.3 second before the QRS waves, and these may or may not represent auricular activity. It is possible that there was actual auricular standstill with a varying independent rate of the auriculoventricular nodal pacemaker producing ventricular contractions alone. The initial deflection of QRS is downward and does not exceed 1 mm. This is followed by an R wave, the height of

which varies between 3.0 and 4.0 mm. The RS-T segment is very slightly elevated (not more than 1 mm.) and ends in a rather sharp inversion of the T wave. The duration of QRS varies between 0.09 and 0.120 second. The Q-T interval varies between 0.36 and 0.40 second. The T wave is definitely inverted, but is never more than 1 to 1.5 mm. deep. (These measurements are not corrected for standardization which was 1 mv. equivalent to 1.2 cm.)

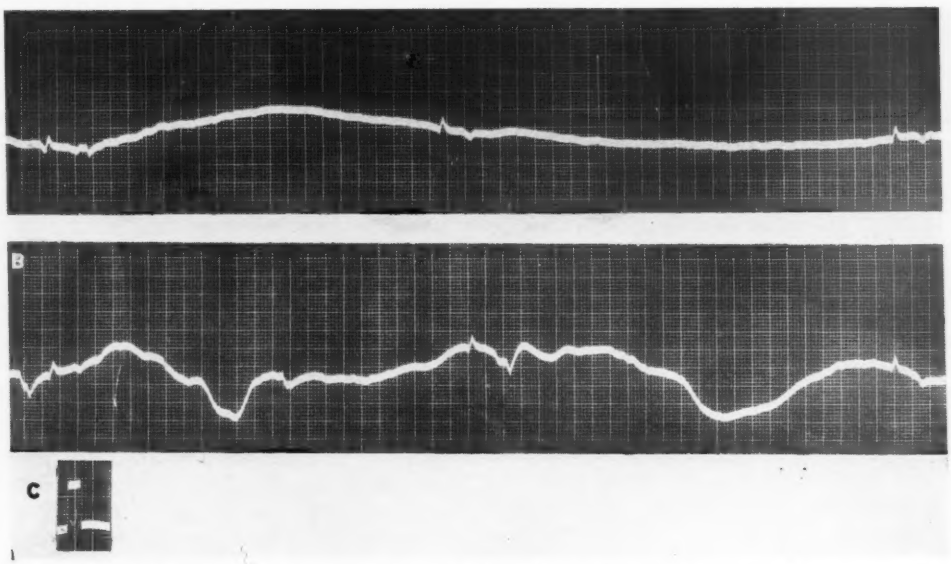


FIG. 3. (*A*) Dorsal lead electrocardiogram of Beluga whale showing a fairly smooth baseline at a time when there was relatively little general muscular activity. There are three heartbeats at a rate of 12.5 per minute. See text for full description. (*B*) Dorsal lead electrocardiogram of the Beluga whale during greater muscular activity. (*C*) Standardization: 1 mv. equals 1.2 cm. Time equals 0.20 and 0.04 second.

DISCUSSION

It is assumed that the whale studied was in good health as evidenced by his community behavior and by the postmortem observations. The electrocardiogram was of a wounded and excited animal which was desperately diving and thrashing about, towing a boat of the estimated weight of 1200 pounds through cold, brackish salt water. There was considerable variation in the R-R interval. This change of rate can quite possibly be attributed, as suggested by the studies of Irving and his associates[5–8] on the seal and on man, to a vagal effect incident to diving. Other investigators have shown that in diving mammals, when it is necessary to suspend respiration and there is a necessity to curtail oxygen consumption or conserve oxygen stores, the heart rate may be reduced to as much as one tenth, the circulation through the muscles is greatly reduced apparently by vasoconstriction, and lactic acid accumulates in the muscle but not in the general circulation. Furthermore, it has been shown that simultaneously the blood flow to the brain is unchanged or increased. It seems reasonable to assume that the frequent or perhaps complete failure of the P waves to appear can be a vagal effect also. The factor of diving may explain the slower rate (15 per minute) in the Beluga whale while submerged as compared with the higher rate (30 per minute) in the elephant whose heart is much larger.

Our inability to obtain a unipolar type electrocardiogram is not clearly explained,

but might possibly be accounted for on the basis of the reduced salt content of the mixture of sea water and muddy water from the river, rather imperfect grounding facilities aboard the skiff, and heavy insulation of the whale itself.

The main value of this experiment is the development of a technic for securing tracings on whales in their native habitat. It is anticipated that this method, or some modifications thereof, will be employed on similar animals of greater size and correspondingly larger hearts.

Summary

A dorsal lead electrocardiogram has been taken of an adult male Beluga whale in Alaskan waters for the first time. It showed a heart rate of 12 to 24 while the animal was engaged in excited and strenuous effort most of the time. The auricular activity was obscured if present at all; there may have been actual standstill of the auricles with escape of the auriculoventricular nodal pacemaker. The QRS and T waves were of low voltage, probably due to the remoteness of the electrodes from the heart and their proximity to one another.

Thus it has been shown that it is possible to obtain an electrocardiogram of a whale in its natural environment. The general characteristics of a single, bipolar, dorsal electrocardiogram are similar to those of other mammals.

Acknowledgments

The authors gratefully acknowledge the cooperation of many individuals and business firms without whose material assistance and advice this experiment could not have been attempted. Among those to whom we are especially indebted are: Dr. Frank N. Wilson, Ann Arbor, Mich., and Dr. Laurence Irving, Arctic Research Center, Anchorage, Alaska, for their invaluable technical advice; Dr. William J. Mills (Surgeon), Mr. Don Cooper (Superintendent), Mr. Louis Delebecque (Transportation), Louis de-Vieu (Supplies), Francis (Jeff) Davis (harpooner), Joe Clark (motorboat operator), of the Alaska Packers Association for their great skill, hospitality, cooperation and active assistance, as well as for the use of many others of their staff and various pieces of equipment at Clarks Point; Seattle Radio Supply Company for electrical equipment; Mr. Wayne Quinton of the Medical Instrument Shop, University of Washington School of Medicine, for invaluable assistance in the design and manufacture of the harpoon heads; and Mr. Garry Lewis, Sanborn Company, Seattle, Washington, for his generous and enthusiastic application of time and energy in making preparations for the expedition.

Addendum

In January, 1953, at the kind invitation of the Scripps Oceanographic Institute of the University of California at La Jolla, and with their help and that of the United States Navy, and of Francis (Jeff) Davis, the authors attempted to obtain an electrocardiogram of one of the large gray whales, 30 to 50 feet long, off the coast of Southern California north of San Diego, using a modification of the technic that was successful in the case of the Alaskan white whale. Although several gray whales were encountered and approached, it was not possible to get near enough to use the electrodes thrown by hand harpoon. Another attempt will be made at a later date by the use of different technics.

Sumario Español

En el curso de nuestro estudio de la anatomía comparativa y la fisiología del corazón mamífero se manifestó necesario el desarrollar un método de obtener un electrocardiograma en el mamífero más grande de todos. Por ser asequible, la ballena pequeña Beluga de los mares del norte fué el primer objeto de este estudio, antes de obtener un trazado de una ballena grande que es el objetivo final del estudio. Este trabajo describe el proceso de obtener el electrocardiograma y presenta también el trazado obtenido.

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Embolic Occlusion of Patent Foramen Ovale

A Syndrome Occurring in Pulmonary Embolism

By G. B. Elliott, M.B., and R. E. Beamish, M.D.

In the presence of a patent foramen ovale, pulmonary embolism may result in a right-to-left interatrial shunt which serves to alleviate the effects of the embolism. When the shunt is occluded by a subsequent embolus, sudden death occurs. The clinical and pathologic features of the syndrome are described.

RECENTLY two cases of pulmonary infarction were encountered which showed atypical clinical manifestations. At autopsy, in each instance a thrombus was found straddling a patent foramen ovale, suggesting a functional shunt during life. It is the purpose of this paper to describe the associated syndrome.

Although some 48 instances of a clot caught in a patent foramen ovale have been described since 1859, there has been no uniformity in terminology or clarity of thought regarding it. Many have been described as "paradoxic embolism" and a recent paper[1] refers to it as "Lodging of an Embolus in a Patent Foramen Ovale." The term "paradoxic embolism" was originally devised by Zahn[2] in 1885 to describe a condition in which emboli derived from the systemic venous system reached the systemic arterial system by passing through an abnormal communication between the chambers of the heart. It is apparent that this occurs when a small thrombus passes through a cardiac septal defect, but this is quite different from the event of a large thrombus being caught in the septal defect with consequent occlusion of its lumen. Thus embolic occlusion of a patent foramen ovale is to be distinguished from "paradoxic embolism" which may or may not accompany it.

Autopsy specimens showing a thrombus caught in the act of traversing an atrial septal defect have been of interest only as anatomic confirmation that paradoxic embolism does occur. Many of the patients were thought to have died of "further pulmonary embolism," and the surprise finding of a thrombus occluding a patent foramen ovale has been regarded as a coincidental occurrence. According to Vimtrup,[3] the earliest account of such a condition is that of Wallman,[4] who in 1859, wrote: "I have found a tough clot resembling thrombus in the auricular and ventricular cavities of three hearts, in which a firm cord of thrombus passed through a valvular patency of the foramen ovale from the left into the right auricle. In these three instances one supposes that at the end of life, when auricular pressure relationships may alter, a transfer of blood from one to another auricle might occur." Despite the implication that such an occlusion might have had serious hemodynamic consequences, it does not appear that these have been recognized although both Kyber[5] and Johnson[6] briefly alluded to the possibility.

Case Reports

Case 1. C. M., a 66 year old male with a previously diagnosed duodenal ulcer, was admitted to the Winnipeg General Hospital on Nov. 4, 1950, with an acute gastrointestinal hemorrhage. He received several transfusions and improved; a few days later, however, bleeding recurred and it was decided that a gastrectomy should be performed. Because he had had an infected hematoma of the left leg following injury three years previously, his legs were carefully examined and no evidence of thrombophlebitis found. He was prepared for surgery and on November 14, a partial gastrectomy was carried out uneventfully. His condition postoperatively was good and he was up in a chair the day following operation. Progress continued uninterruptedly until the evening of November 19 (fifth postoperative day). At 10:40 p.m., while on a bed

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Presented before the Canadian Heart Association, Lake Louise, Alberta, June 10, 1952.

pan, he developed sudden severe dyspnea without pain. He was seen to be pale and cyanosed; the heart was rapid (130 to 150) with a triple rhythm and blood pressure was 70/40. Neck veins were moderately distended. Clinical examination of the lungs and heart was negative. It was thought at first that he had either a concealed internal hemorrhage or a massive pulmonary embolism.

It soon became clear that his shocked state was not due to hemorrhage, and he was treated for a pulmonary embolism with oxygen, blood, intravenous procaine and heparin. An emergency electrocardiogram was taken, but, apart from tachycardia, it was not remarkable. During the night his condition remained unchanged: he was pale; cyanosis persisted in spite of oxygen; he perspired profusely; his skin was cool; his heart rate remained rapid and his pulse small. Blood pressure after four bottles of blood, remained at 75/60, and he was almost anuric. Next morning (November 20) the electrocardiogram was repeated and showed no change from the evening before. (See fig. 1.) There was little change in this

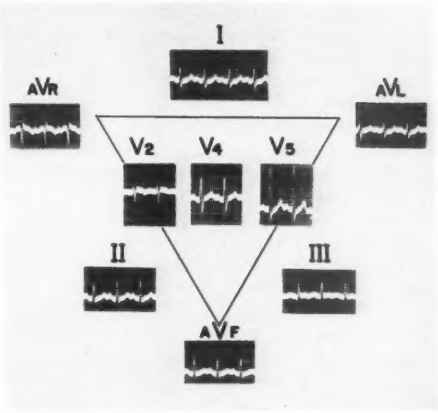

FIG. 1. Electrocardiogram of case 1. Apart from tachycardia, the tracing is within normal limits. (On vector analysis, record is consistent with, but not diagnostic of, pulmonary embolism.)

FIG. 2. View of opened atria in case 1. The intracardiac embolus is caught in the act of traversing an atrial septal defect, and the end projecting into the left atrium is intact.

state throughout November 20 and November 21, and his sensorium remained clear. Considerable misgivings were felt about the working diagnosis of pulmonary embolism when he neither got worse nor better as time wore on. Late in the evening of November 21, he became more dyspneic and the blood pressure fell to 50/40. A continuous adrenaline drip was started, but his general condition deteriorated and he died at 1:40 a.m., November 22, 50 hours and 45 minutes after his collapse.

An autopsy eight hours later showed deep cyanosis of face and limbs. Fluid blood distended the right atrium and ventricle so that they formed three-fourths of the presenting surface of the heart. An embolus 10 cm. long, arching up from the opening of the inferior vena cava, was tightly impacted without adhesion in a 1.0 cm. diameter patency of the foramen ovale (fig. 2). The venous end was broken and laminated. In contrast, 3.0 cm. of firm unbroken embolus tapering to a rounded tip projected into the left atrium. A hemorrhagic infarct 3.0 cm. in diameter occupied part of the lower lobe in each lung. All pulmonary arteries except the main branch to the right middle lobe, one tertiary division to the right upper lobe, and two to the left upper lobe, were occluded by brittle, moderately adherent emboli. Considering that there are usually 10 tertiary subdivisions of the pulmonary artery, this represents about 50 per cent occlusion of the arterial tree. Lightly adherent antemortem thrombi up to 15.0 cm. in length were expressed from each femoral vein. Microsections of viscera confirmed the character of emboli and infarcts.

Comment. The prolonged unexplained survival of this patient in an unusual state, together with the remarkable embolic occlusion of a possibly large right-to-left shunt in the heart, suggested that the patent foramen ovale served as a palliative shunt and that its occlusion was the precipitating cause of death. This interpretation led to a review of clinical features of cases which had been reported from a pathologic viewpoint. During this investigation, a second case, complicated by a paradoxic air embolism was observed.

Case 2. Mrs. C. C., a 24 year old primipara, was delivered on June 16, 1951, and developed a persistent systemic postpartum infection after removal of retained placenta. She was admitted to the Winnipeg General Hospital on July 19 with acute diffuse peritonitis and paralytic ileus. Slow symptomatic improvement followed intubation, antibiotic therapy and intravenous feeding. On August 8, pulmonary embolism was diagnosed, following an attack of sudden, substernal, breath-catching pain with dullness in the right lower lobe posteriorly. Two days later clear fluid aspirated from a right pleural effusion yielded no growth or culture. By August 14 it was evident that the peritonitis had localised with pelvic and subphrenic abscess formation.

The right twelfth rib was resected at an elective operation for drainage of the latter on August 17. While separating adhesions manually over the dome of the liver, several hundred cubic centimeters of clear yellow fluid gushed forth, and the surgeon believed he had inadvertently entered the right pleural cavity. The patient immediately blanched, respiration ceased, and the radial pulse became feeble, then imperceptible. After hearing an initial precordial churning murmur, the anesthetist heard no heart sounds and blood pressure was unobtainable. A new epigastric incision showed apparent cardiac standstill; direct cardiac massage gradually restored beating after a three minute pause. Further exploration was abandoned. The pulse was again found to vanish when turning the patient on her right side during dressing, to reappear when supine. A portable radiograph showed a right pneumothorax. No intracardiac translucencies, as described by Taylor,[7] were distinguishable on review. Her condition deteriorated two hours later and 500 cc. of air were aspirated and closed pleural suction drainage set up. Convulsive twitching of limbs was noticed in the next hour. Deep coma persisted with profuse perspiration, ashen cyanosis unrelieved by oxygen, labored respiration at 30 per minute, irregular tachycardia of 150 per minute, and a blood pressure of 160/100. The blood pressure fell abruptly 45 hours after operation to 100/80 and there was steady deterioration to death 40 minutes later.

At autopsy three hours later, the cranial cavity was first explored with care, then the thoracic cavities opened under water, using the technics recommended to demonstrate air embolism. Bubbles up to 2 mm. diameter were enmeshed in postmortem clot in the sagittal sinus, with minute bubbles in the superficial cerebral vessels and emissary veins in all areas. The brain showed no gross changes. A right pneumothorax at atmospheric pressure was detected by needle exploration with manometric attachment. A few tiny bubbles were present in branches of the coronary artery over the anterior surface of both ventricles. Early fibrinous pericarditis was present. Some bloody froth occupied the ventral parts of the right ventricle and pulmonary artery with small amounts in the right atrium. A nonadherent antemortem thrombus, 5.3 cm. long and 0.3 cm. in diameter was held in a slit-like anterior valvular patency of the foramen ovale 0.5 cm. in diameter. Some 1.8 cm. projected into the left atrium, neither rounded end showing fragmentation (fig. 3).

The completely atelectatic right lung showed fibrinous pleuritis and two brownish friable infarcts, 3.0 and 1.8 cm. diameter in the lower lobe, the larger being septic. The latter lay posteromedially, an-

chored superiorly by a band-like adhesion. A tear beginning in this attachment extended for 3.5 cm. through the infarct and intact lung to end in mediastinal pleura. Blue ink injected into the inferior vena caval termination, after clamping off the heart, returned through the medial end of this tear, but the communicating vein was not identified. In the depth of the packed laparotomy wound was a 6.0 cm. split of muscle forming the posterior part of the right diaphragmatic dome. This appeared to be the site of accidental entry into the pleura. The remaining lesions were an unopened right subphrenic abscess, two small septic hepatic infarcts posterior to this abscess, fibrinous peritonitis, small septic infarcts in both kidneys, and bilateral tubovarian abscesses. Friable, free, septic, antemortem thrombi lay in the left common iliac, left internal hypogastric, and right femoral veins. A hemolytic, coagulase-positive staphylococcus was isolated from the septic sites, but no gas-producing organisms were found. Microscopic examination confirmed the character of the lesions.

FIG. 3. View of intracardiac embolus in case 2, found straddling an anterior valvular patency of the foramen ovale. The larger portion lies in the right atrium and both ends are intact.

Comment. The massive atelectasis of the right lung, together with infarction, constituted a major obstruction to the pulmonary circulation during life. In this instance, deep coma probably due to cerebral air embolism replaced the clear consciousness shown by the first case. The observed clinical sequence was otherwise similar, peripheral paradoxic emboli being an autopsy finding. In addition to being of interest in connection with the syndrome under consideration, this case has some significance in relation to paradoxic air embolism. The physiologic basis of air embolism, both in venous and arterial forms, has been reviewed by Durant[8] while Merkel[9] has reviewed paradoxic air embolism, a very rare variety.

In this patient, the clinical collapse with a classic churning murmur over the right ventricle, and sudden alleviation of a second collapse by changing the patient from her right side to a supine position during dressing, were diagnostic of venous air embolism. The prolonged coma and clonic spasms are features of subsequent arterial air embolism. We do not know with certainty at what intervals air entered the arterial or venous circulation, for the patient survived 45 hours in deep coma. It is questionable whether air bubbles can pass through the pulmonary arteries into the systemic arterial circulation. This case is the only instance of which we are aware in which the presence of a right-to-left interatrial shunt during life is confirmed by an embolus in situ in the foramen ovale. It is thus reasonable to

assume that this shunt was the route of the arterial air emboli.

Discussion

Evidence for the anatomic and physiologic basis of paradoxic blood flow from right-to-left atrium has been presented in several reviews.[6, 10] After birth the tension in the right atrium falls, and the higher pressure in the left atrium now becomes sufficient to establish competence of the valvelike flap over the foramen ovale. Lesions reversing this adult atrial pressure relationship re-establish the fetal shunt where patency persists. Foremost among such lesions are pulmonary embolism and infarction, where the following sequence develops: (1) pulmonary embolism occurs and the pressure in the right atrium rises; (2) when this exceeds the left atrial pressure, blood flows through the foramen ovale. Clearly a subsequent embolus arriving in the right atrium may then, if small, pass into the left atrium and arterial circulation, but if large, impaction results.

In cases of massive pulmonary embolism, it has been supposed by Johnson[6] that "a patent foramen ovale would be instrumental in prolonging life by providing a much needed shunt." Kyber[5] thought of it as "a sort of emergency outflow." The behavior of case 1 indicates that this is so, and in addition that when this shunt is blocked, death is precipitated. The clinical course of this patient would appear to constitute a syndrome as follows:

1. A clinical sequence of collapse from pulmonary embolism, incomplete recovery, sudden deterioration and precipitate death.

2. The recovery phase in its most recognizable form is characterized by a state of prolonged survival with greyish pallor, moderate cyanosis unrelieved by oxygen (because of the shunt), profuse perspiration, persistently low blood pressure, a fast thready pulse, and only moderate venous distention. Peripheral paradoxic embolism may occur in this phase.

3. Absence of electrocardiographic changes diagnostic of acute cor pulmonale both in the initial collapse and recovery phases, presumably due to the decompressing action of the shunt. (See fig. 1.)

4. At death cyanosis and venous distention are conspicuous due to acute cor pulmonale supervening when the decompressing shunt is blocked.

Table 1 presents an analysis of the 29 cases of embolic occlusion of foramen ovale by thrombus occurring after 1926. The previous 18 reports are exclusively in the older European literature not generally available, and only 10 contain clinical detail. It is seen that there are 14 cases (cases 1–14) which show the clinical sequence of the syndrome described. However, five (cases 10–14) of these were complicated by cerebral embolic lesions, and rapid death is not spectacular in patients already comatose. Nevertheless, Young's[11] case (case 12) died suddenly, and Lindley[12] noted that "death occurred suddenly while stuporous" in his case (case 13). In our case 2 (case 14), there was terminal worsening in the last 40 minutes, during deep coma. Vimtrup's[3] case 2 (case 11) died in coma one and one-half hours after cerebral embolism, and Wittig's[13] case (case 10) shows a closely similar termination. In contrast, the 12 cases of coma due to presumptive paradoxic cerebral embolism, reported after 1930,[10, 14-18] and not associated with foraminal occlusion, do not show this abrupt demise. Most survive for weeks after the cerebral episode, the shortest survival being eight hours. There is only one instance of sudden death and this was due to an obvious massive pulmonary embolism. Thus it is apparent that cerebral embolism, per se, is not a decisive cause of precipitate death; it is rather our belief that the sudden demise is due to the intracardiac embolism.

Of the remaining 15 cases the demise is undescribed in five (cases 15–19), three of whom had paradoxic cerebral embolism of comparatively short duration. Five cases (cases 20–24) showed sudden or precipitate death without apparent clinical pulmonary embolism. However, of these, Elliott's[19] case (case 20) showed a septic infarct in one lung, and Merkel's[9] case (case 22) showed old as well as recent pulmonary emboli, while recent

TABLE 1.—*Cases of Embolic Occlusion of Patent Foramen Ovale Reported after 1926*

Author		Pulmonary Embolism or Infarction Clinical: Autopsy		Recovery Phase Duration	Peripheral Arterial Embolism	Length and Mode of Terminal Collapse
1. Barnard[23]		+	+	½ day	+	Sudden death while talking.
2. French[24]		+	+	23 days	−	15 minutes of acute clinical symptoms.
3. Taylor[28]		+	+	21 days	+	"Shortly after" acute exacerbation.
4. Koritschoner[27]		+	+	3 hours	−	Sudden death.
5. Ingham[16]	III	+	+	4 days	+	"Suddenly became worse and died."
6.	IV	+	+	2 days	−	Sudden exacerbation and death.
7.	V	+	+	½ day	−	Sudden death.
8. Vimtrup[3]	I	+	+	14 days	−	15 minutes of acute symptoms.
9. Present series	I	+	+	2 days	−	2½ hours—died in acute exacerbation.
10. Wittig[13]		+	+	14 hours	+ (Brain)	Unstated—died 2 hours after cerebral infarction.
11. Vimtrup[3]	II	+	+	1¾ hours	+ (Brain*)	Died after brief coma.
12. Young[11]		+	+	7 days	+ (Brain*)	Sudden death.
13. Lindley[12]		+	+	12 days	+ (Brain*)	"Sudden death while stuporous."
14. Present series	II	+	+	2 days	+ (Brain Air)	40 minutes—died in coma.
15. Jones[29]		+	−	12 days	+ (Brain)	Died on 11th day of coma.
16. Ingham[16]	I	+	+	10 days	+	Unstated.
17.	II	+	+	7 days	+ (Brain)	Died on 4th day of hemiplegia.
18. Robinson[1]		+	+	3 days	−	Unstated.
19. Johnson[6]	I	+	+	2 days	+ (Brain)	Unstated—died 1 day after cerebral infarction.
20. Elliott, T. R.[19]		−	+		−	Sudden death.
21. Wilson[20]		−	+		−	5 minutes—sudden death.
22. Merkel[9]		−	+		+	Sudden death.
23. Hirschboeck[30]		−	+		−	35 minutes of acute symptoms.
24. Ingham[16]	VI	−	+		−	Sudden death and cyanosis.
25. Wolff & White[21]	XI	Not stated		Not stated	? (Heart)	Sudden death.
26. Geipel[22]	I	Not stated	+	Not stated	−	"Died a few days after myomectomy."
27.	II	Not stated	+	Not stated	−	Not stated.
28.	III	Not stated	+	Not stated	−	"Death from pulmonary embolism."
29.	IV	Not stated	+	Not stated	−	"Death from pulmonary embolism."

* Clinical evidence.

emboli were present in the remainder of the group. In addition, Wolff and White (case 25) make a very short note[21] in which the condition of the lungs is not specifically mentioned and "embolism of the descending branch of the left coronary artery" is also described. Finally, in Geipel's[22] four cases (cases 26–29) there is insufficient clinical information on which to base any opinion. In summary, out of the 29 cases, 14 fall within the general clinical pattern described, five conform so far as their clinical detail goes, five showed sudden death alone, and five lack adequate history for appraisal. No striking exceptions occur.

Because these cases have nearly always complicated pulmonary embolism, death has been ascribed to "further pulmonary embolism" without direct proof. From the foregoing discussion, it would seem obvious that death was, in fact, due to the intracardiac clot, as has been tentatively suggested. That such a clot is indeed a terminating event is supported by several additional observations. Barnard's[23] reported circumstances make it likely that the thrombus passed into the foramen ovale "as the heart was making its last beats," and French[24] noted "it is evident there was no time for the embolus to be broken and thrown into fragments into the arterial circulation." In Young's[11] case, the aorta also "contained an embolus which extended from the heart itself throughout the aortic arch." There are 21 detailed descriptions of the impacted embolus of the foramen ovale since 1925. The thrombi average 9.7 cm. in length, ranging up to 27.5 cm. but in no case is there evidence of fracture of the end in the left atrium. This feature is present even in those cases associated with peripheral arterial emboli. It is unlikely that brittle antemortem thrombi of such length could endure long in the atria without fracture. Of those dependent through heart valves, only a few pressure grooves are mentioned. It is noteworthy that 51.7 per cent (15 of 29 cases) showed no paradoxic emboli outside the heart itself. Thus, it seems clear that the heart stops within a few beats of the foraminal occlusion.

It is advantageous at this point to compare relevant features of uncomplicated pulmonary embolism. Using graded pulmonary arterial occlusions in cats, Haggart and Walker[25] found no corresponding graded severity of symptoms. Although pulmonary arterial pressure rose, cardiac output was well maintained up to 60 per cent occlusion. Beyond this, a dramatic fall in cardiac output took place, with lowered systemic blood pressure and arterial oxygen saturation. In a clinical study, Thompson and Evans[10] showed that depletion of the pulmonary circulation by more than a third was necessary to reverse atrial pressures, and that a sudden depletion of 50 per cent or more resulted in death, perhaps sudden, but within 30 minutes. In case 1 (case 9) although at least 50 per cent of the pulmonary arterial tree was occluded by adherent thrombi, death did not occur for over 50 hours. In table 1, the period of apparent recovery or palliation from pulmonary embolism ranges from one hour to four days. Evoy[26] points out that in 246 fatal cases of pulmonary embolism, 92 per cent were dead within 24 hours, and 69 per cent were dead within one hour. Thus it is apparent that precarious survival for long periods is not a feature of uncomplicated pulmonary embolism. The essential difference between this and pulmonary embolism with patent foramen ovale is the decompression provided by the interatrial shunt. That the shunt does function to decompress is supported by electrocardiographic evidence available in four cases (cases 8, 9, 11, 13). In pulmonary embolism, the characteristic electrocardiographic picture is dependent on the production of an acute cor pulmonale. In the four cases associated with a patent foramen ovale, these changes have not been observed presumably because the right atrium was decompressed into the left until the terminal foraminal occlusion.

The influence of other factors beside relative atrial pressure may be considered. "Pencil patency" (0.7 cm. diameter) of the foramen ovale persists in 1 per cent of adults of the average age at which confirmed paradoxic embolism occurs (51.5 years).[10] However, reports of embolic occlusion of the foramen ovale are excessively rare. It seems to us that this infrequency depends on the relative sizes of the shunt and of the embolus rather than on the "element of chance." The average diameter of the foramen ovale in cases reported after 1925 is 0.68 cm. and in 80 per cent the source of the emboli was in veins of pelvis or leg where the caliber of thrombi is likely to approximate that of the foramen.

Johnson[6] believed that "the magnitude of the stream through the foramen ovale might well be as great as through the pulmonary artery." That it may be even greater is suggested by the situations of the impacted foraminal emboli reported since 1925. In only two instances did one pass through the tricuspid valve (cases 27, 28), while in four instances it passed through the mitral valve

(cases 1, 2, 16, 21), and in three others long emboli remained coiled up in the right atrium (cases 4, 20). In other words, the main flow was probably through the shunt.

We know of no case of comparable embolic occlusion of a patent interventricular septal defect. For reversal of interventricular flow to occur, a degree of pulmonary obstruction sufficient to cause immediate death would seem necessary. Thus, although the association of cerebral abscess with patent interventricular septum has been recorded at intervals since 1814,[31, 32] confirmation of its relationship as an embolic syndrome is lacking. While embolic occlusion of a patent foramen ovale may be rare, the lifesaving effect of the interatrial shunt may be commoner. It is conceivable that some patients who recover from massive pulmonary embolism do so because of this unrecognized mechanism.

Summary

1. Two instances of a thrombus having been caught passing through a patent foramen ovale are described.

2. This is defined as "embolic occlusion of patent foramen ovale," reserving the term paradoxic embolism to describe peripheral arterial embolic occlusions by venous thrombi.

3. It would appear that death in such cases is precipitated by acute cor pulmonale as a consequence of sudden obstruction of a decompression shunt between right and left atria and not to further pulmonary embolism as has been supposed.

4. The concomitant clinical syndrome is described. Of the 24 cases reported since 1925 on which there is sufficient data available, all conform to this pattern. The apparent exceptions are discussed.

5. The full clinical sequence consists of pulmonary embolism followed by a variable period of improvement (the "palliative shunt" phase), and finally sudden death with conspicuous cyanosis, when the shunt is occluded. In its most recognizable form, the shunt phase is characterized by pallor, cyanosis unrelieved by oxygen, hypotension, profuse perspiration, moderate venous distention, and absence of electrocardiographic changes seen in acute cor pulmonale. During this phase, peripheral paradoxic embolism may occur.

6. In one of our cases, the foraminal occlusion was preceded by paradoxic air embolism. This is apparently the first instance of proven paradoxic air embolism, where the presence of a right-to-left interatrial shunt during life has been confirmed.

Acknowledgment

The authors are indebted to Dr. J. W. Rennie for referring the first case and to Dr. M. B. Perrin for permission to publish the second case; to Prof. Joseph Doupe, University of Manitoba, for helpful criticism, and to Prof. Robert Bayley, University of Oklahoma, for reviewing the electrocardiogram of case 1.

Sumario Español

En la presencia de un foramen ovale patente, embolismo pulmonar puede producir un "shunt" inter-auricular de derecha a izquierda que alivia los efectos del embolismo. Cuando el "shunt" es ocluido por un embolo subsiguiente, muerte súbita ocurre. Los aspectos clínicos y patológicos del síndrome se describen.

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CLINICAL CONFERENCES

EDITOR: EDGAR V. ALLEN, M.D.

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Electrocardiograms of Deceptive Form in Ventricular Hypertrophy

BY CHARLES E. KOSSMANN, M.D.

(Since 1911, a monthly clinical or clinical pathologic conference has been held for the clinical clerks—volunteer third and fourth year medical students—and staff of the oldest known clinic for the care of ambulatory cardiac patients in existence.[1] At each of the conferences held on Oct. 30, 1952 and Nov. 20, 1952, a case was presented which displayed during life an electrocardiogram with a configuration quite the opposite of what might be expected from the type of ventricular hypertrophy found after death. Since in one instance the hypertrophy was of the right ventricle and in the other of the left, the fortuitous and instructive coincidence seemed worth recording especially for the purpose of re-emphasizing the undesirability of making anatomic deductions from a purely physiologic method. The proceedings of the two conferences have been condensed into one.)

DR. KOSSMANN: Early in your work in the clinics and on the wards you heard the word "incidence" used repeatedly. Briefly it describes who gets a disease where, when, and how often. It is customary to talk of the frequency component of incidence of a disease usually in terms of a percentage of a susceptible population, or of a death rate. The incidence of a specific phenomenon is usually quoted as a percentage of the cases that will display it. This "incidence" is valuable information to have as can easily be demonstrated. For example, when a right bundle-branch block is observed in an electrocardiogram of a patient born and bred in New York, Chagas' disease of the heart need not be given a second thought because that disease is unknown here. On the other hand if we were physicians in certain parts of Brazil, it would be seriously considered in the differential diagnosis. In each instance a knowledge of incidence of a disease and of a phenomenon in it leads to a correct diagnosis.

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But incidence, especially of phenomena, also misleads the clinician. This seems to be especially true if the frequency of a particular phenomenon in a disease is fairly high—let us say 70 per cent. There is a great natural tendency to underestimate the significance of the other 30 per cent in which the phenomenon is known to be absent. Further, the occasional or frequent occurrence of it in another disease is often lost sight of completely.

In the two cases about to be presented, the phenomenon in question was electrocardiographic, and overweighting of it, on the basis of known incidence, in the over-all appraisals resulted in some confusion, at least in the beginning, regarding the exact anatomic cardiac diagnosis in each.

Mr. Lehrer will present the first case.

CLINICAL CLERK LEHRER: Patient A. A. was a divorced, unemployed shoemaker at the time of his death in congestive heart failure at the age of 63 years.

He had "always" had a mildly productive morning cough but the only significant past respiratory disease was influenza in 1918 when he was 29 years old. As a shoemaker he was exposed to dust while sanding leather by hand for a period of four years. He also had used sandstone for grinding carpenter's tools for some 20 years. He smoked a pack of cigarettes a day.

At 41 he had a penile chancre which was treated for six months with intravenous and intramuscular injections in another hospital. About this time he was first admitted to Bellevue Hospital for swelling of the ankles. Treatment consisted of rest in bed and a salt free diet. The swelling subsided but recurred with physical activity. He was discharged after two weeks.

At 50 an appendectomy was performed under nitrous oxide and ether anesthesia at Bellevue Hospital. A notation was made of exertional dyspnea and edema for some time. An electrocardiogram showed normal sinus rhythm with no deviation of the electrical axis of QRS; it was not abnormal in any respect. A Wassermann test was negative.

At 58 he came to the medical clinic complaining of exertional dyspnea, edema, headache, dizziness, and weakness. Evidence of heart failure was present in the form of rales at both lung bases, an enlarged liver, and edema. Clubbing of the fingers was noted. An electrocardiogram displayed normal sinus rhythm with left axis deviation of QRS but was not otherwise beyond normal limits. X-ray showed questionable cardiac enlargement and some irregular shadows in the bases interpreted as congestion. He was treated for a few months with digitalis and diuretics without improvement. He discontinued taking these drugs in August 1947.

His complaints worsened so that he sought readmission to the hospital in December 1948. He showed little evidence of congestive failure other than edema and rales in the lower parts of the lungs which could be made to disappear with coughing. Additional findings were an inequality of the radial pulses with a blood pressure on the right of 122/70, and on the left of 90/80, minimal sclerotic changes in the retinal vessels, and an increased anteroposterior diameter of the chest. The patient was quite obese (weight 185 pounds, height 62 inches). As on previous examinations the heart sounds were distant, the second pulmonic sound was questionably louder than the second aortic sound, and the electrocardiogram displayed left deviation of the QRS axis (fig. 1). The venous pressure was 95 mm. H_2O. His response to digitalis and mercurials was poor. The impression was that most of his difficulty was pul-

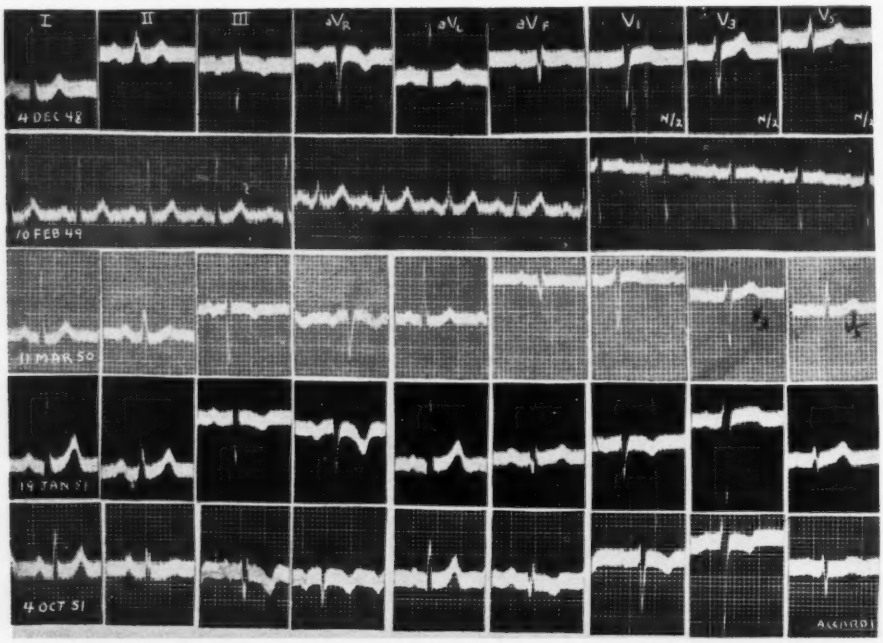

FIG. 1. Electrocardiograms of patient A. A. recorded over a period of approximately three years. On Feb. 10, 1949, only leads I, II and III were recorded. On the other dates there were, in addition, the augmented unipolar extremity leads (aV_R, aV_L, aV_F) and the unipolar precordial leads V_1, V_3 and V_5 made with the string sensitivity at half normal (1 mv.=0.5 cm.). To be noted particularly are the changes in T wave over a period of time in leads aV_F, V_1 and V_3. Time lines occur every 0.04 second.

monary, that obesity contributed to his dyspnea, and that he had an anomaly of the arteries to the left arm.

From January 1949 to the time of his death on Feb. 20, 1952 he was observed in the Cardiac Clinic, and had no less than six additional admissions to the hospital. One of these was for a febrile episode treated successfully with systemic and aerosol antibiotics. The others were for progressive diminution of pulmonary and probably cardiac reserve. Digitalis therapy was reinstituted on several occasions to a point of easily reached toxicity after which the patient would refuse to take the drug. The therapeutic response was never impressive. On one admission cardiac catheterization was done (March 24, 1949) with the results shown in table 1. Briefly there was a slight elevation of pressure in the lesser circuit and a normal cardiac output. Both were increased by exercise. The oxygen saturation of the blood fell after effort.

An important complaint beginning in October 1949 was epigastric and subxiphoid pain on effort, not relieved by nitroglycerin. From that point on tachypnea, tachycardia, and cyanosis were progressive. There was a gradual loss in weight of about 40 pounds. Electrocardiograms showed an inversion of the T wave in leads from the right side of the precordium beginning in January 1951 but no change in the axis of QRS (fig. 1). Chest x-ray films did not change remarkably. The pulmonic second sound was now persistently louder than the aortic second. The venous pressure rose to 152 mm. H_2O but decholin and ether circulation times were normal (15 seconds and 8 seconds, respectively, on Jan. 20, 1951). He was finally transferred to Goldwater Memorial Hospital for chronic hospital care on Oct. 10, 1951.

At the chronic disease hospital extensive pulmonary functional studies were done while the patient received 206.5 mg. of adrenocorticotropic hormone between Nov. 27, 1951 and Jan. 16, 1952. Results of these are summarized in table 2. By way of summary, the adrenocorticotropic hormone at first caused euphoria and relief of the epigastric pain, along with some improvement in pulmonary function. However, he finally became irritable and unmanageable. Complications included a pneumonitis on January 22 which responded to penicillin, a herpes zoster in the distribution of the right seventh intercostal nerve on January 30, and a mycotic stomatitis. Another febrile episode with leukocytosis and dehydration occurred on February 17. He was improving slightly when he died suddenly on Feb. 20, 1952.

Between 1947 and 1952 his hemoglobin was 14.5 to 17 Gm., and the red blood cells from 4.74 to 7.0 million per cubic millimeter. The hematocrits during the last weeks of life were approximately 54. Urinalyses, blood chemistries, and serum electrolytes were not unusual except for some hyponatremia and hyperkalemia terminally.

TABLE 1.—*Hemodynamic Data on Patient A.A. Collected on March 24, 1949*

	Normal Values	Observed			
		Rest	Postexercise		
			0.5 min.	2 min.	5 min.
Pulmonary artery (mm. Hg)	18–34	39 (30)*	59 (42)	55 (38)	40 (29)
	5–10	19	33	27	21
Right ventricle (mm. Hg)	18–34	40	59	53	41
	1–3	5	6	3	7
Right atrium (mm. Hg)	1–2	5			
Artery (mm. Hg)	120 ± 20	141 (100)	154 (115)	158 (115)	143 (99)
	75 ± 10	75	80	80	75
Heart rate (per min.)	65–85	102	114	108	108
Ventilation volume (L./min.)	6–8	9.3	18.7		
Oxygen consumed (ml./M²/min.)	110–140	111	277		
Arterial oxygen (vols. %)	17–20	18.7	17.3		
Arterial saturation (%)	93–96%	91	84		
Mixed venous oxygen (vols. %)	12–15	14.9	13.4		
A-V oxygen diff. (vols. %)	4–6	3.8	3.9		
Cardiac output (L./min.)	5–6	5.4	13.1		
Cardiac index (L./M²/min.)	2.7–3.4	2.9	7.0		
Syst. periph. resist. (mm. Hg/L./min.)	14–22	18.5			

* Mean pressures in parentheses.

TABLE 2.—*Pulmonary Function (Patient A. A.)*

Period	Date	Weight lbs.	Vital Capacity ml. (3206)*	Total Capacity m¹. (4635)*	Residual Air/ Total Capacity % (31)*	Maximal Breathing Capacity % of predicted (not less than 80)*	Oxygen Inspired Air %	Pulmonary Ventilation L./min./M.² (3.2–4.9)†	Oxygen Consumption ml/ min./M.² (107–165)†	R.Q.	pO_2 Inspired Air mm. Hg	pO_2 Alveolar Air mm. Hg (90–110)†	pO_2 Arterial Blood mm. Hg (90–100)†	pCO_2 Alveolar Air mm. Hg (36–42)†	Arterial Blood Oxygen Saturation %‡ (95–97.5)	Dead Space/ Tidal Air % (30 or less)†
Control (10/11/51 to 11/26/51)		148–153														
	10/24/51	149	1785	3842	54			—	—	—	—	—	—	—	—	—
	11/5/51	151	—	—	—	103 to 123	21	7.99	151	.75	154	90	46	48	80	66
	11/5/51		—	—	—		30	7.60	139	.75	218	160	100	43	97	64
	11/5/51 (Exercise) ¶						21	—	—	—	—	—	41	53	73	—
Therapy with ACTH§ (11/27/51 to 1/16/52)	12/18/51	154	1900	3797	50		—	—	—	—	—	—	—	—	—	—
	12/20/51	154	—	—	—		21	8.36	159	.80	153					
	1/10/52 (Fever 101 F.)	158	—	—	—		21	10.64	193	.81	149	105	63	36	90	56
	1/10/52		—	—	—	102 to 127	30	10.49	187	.75	212	167	104	34	98	56
	1/10/52 (Exercise) ¶		—	—	—		21	14.94	509	.89	148	89	41	53	74	
	1/14/52	157	1744	3872	55		—	—	—	—	—	—	—	—	—	
Control (1/17/52 to (2/15/52)	2/15/52 (Fever 101 F.)	151	—	—	—	108 to 117‖	21	15.50	297	.81	152	88	42	52	74	65

* Predicted value. † Normal range at rest. ‡ Interpolated from standard oxygen dissociation curve. § ACTH kindly provided by Armour and Co. Each daily dose dissolved in 1000 ml. of 5 per cent glucose in distilled water was administered intravenously over a period of 8 to 12 hours. The dosage schedule was as follows: Nov. 27, 28—15 mg.; Nov. 29 to Dec. 3—10 mg.; Dec. 4 to 11—5 mg.; Dec. 12, 13—2.5 mg.; Jan. 14—2 mg.; Jan. 15, 16—1 mg. From Jan. 17 to 20 an infusion without ACTH was given. ¶ Approximately 30 step-ups in one minute on a stool six inches high. ‖ Last test performed on Jan. 18.

DR. KOSSMANN: Dr. Brumlík, you fluoroscoped this patient on several occasions. Will you comment on the radiologic findings both on fluoroscopy and on teleroentgenography?

DR. BRUMLÍK: I first fluoroscoped this man on Feb. 10, 1949. In the frontal view the heart was transverse in position, and although there was a pleuropericardial fat-pad at the apex, nevertheless the heart seemed a little enlarged in its long diameter. In the right anterior oblique view there was a retrocardiac shadow interpreted as calcified glands, and the outflow tract of the right ventricle was bulging anteriorly. The lung markings were accentuated in both fields. On x-ray this had the form of nodulations with some coalescence at the right base. There was not much change in the radiographic picture described while the patient was observed in our clinic (fig. 2).

DR. KOSSMANN: Are there any questions regarding the course of the patient's disease or the findings?

CLINICAL CLERK: Is it likely that the edema for which this patient was admitted to the hospital at 41 was similar to the edema seen in the last few years of his life?

DR. BERGER: I think not. The edema was of two types. When we first saw this man in the clinic it was the nonpitting type often seen in short, obese people, probably on the basis of chronic lymphatic obstruction with excessive subcutaneous fat around the ankles and lower legs. The second, pitting type appeared much later in the course of the disease.

CLINICAL CLERK: What was the epigastric pain on effort ascribed to?

MR. LEHRER: No statement was available in any of the records on the possible cause.

DR. KOSSMANN: I can add a little to the answer. In seeking possible causes of the epigastric pain we were able to demonstrate by further workup a hiatus hernia of the stomach, an osteoarthritis of the dorsal spine, and a gall bladder which on two occasions filled poorly or not at all with dye. None of these disease states seemed adequate, however, to explain the symptom. Coronary insufficiency as a cause was considered, but against it was the failure of the pain to respond to nitroglycerin. Further, although it was worse on effort, the pain was sometimes persistent at rest for long periods of time, particularly toward the end. No convincing explanation was ever forthcoming. It is noteworthy, however, that patients with heart disease secondary to a chronic disease of the lungs will often suffer from lower substernal or epigastric pain. It has been given a variety of names including hypercyanotic angina and pulmonary hypertensive pain.[2] It has been ascribed to dilatation of the pulmonary artery, to coronary insufficiency largely on the basis of arterial oxygen unsaturation, to congestion of the liver, to an unusually low level of the diaphragm with tension on the central and

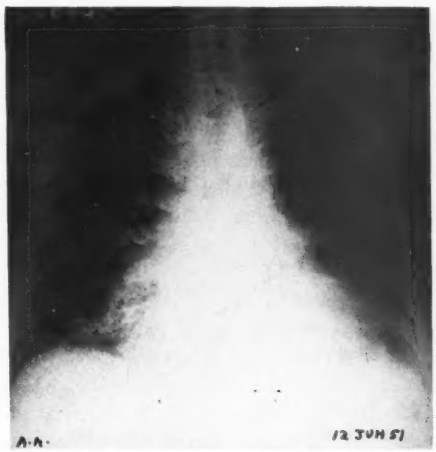

FIG. 2. Patient A. A. Teleroentgenogram made on June 12, 1951, about eight months before death.

other ligaments, to peptic ulcer, and to other causes, most of them difficult to document or indict. The symptom, nevertheless, is real, and most often simulates anginal syndrome except for its long duration.

Dr. Eichna, would you say that the hemodynamic data collected by you about three years before the patient's death make it possible to say, without reference to any other data, that we were dealing with latent pulmonary arterial hypertension from intrinsic pulmonary disease?

DR. EICHNA: Probably yes. The data (table 1) indicate slightly higher than normal systolic and diastolic pressures in the pulmonary artery and in the right ventricle when the patient was

at rest. These pressures, except the diastolic pressure in the right ventricle, were further increased by a degree of exercise which raised the cardiac output approximately two and one-half fold. Other figures indicate that the resistance of the pulmonary vascular bed was increased, but whether by intrinsic vascular disease or by the inability of the left ventricle to increase its output under stress cannot be stated definitely. However, the normal cardiac output at rest and its satisfactory increase with exercise suggest that myocardial failure was not responsible for the elevated pulmonary artery pressures. On the other hand, the somewhat elevated pulmonary artery pressure at rest and its sharp rise with an increase in blood flow (cardiac output), a rise which would not occur in the normal subject, certainly suggests primarily increased pulmonary vascular resistance as the cause. Whether this increased resistance was neurogenic in origin or due to organic pulmonary vascular disease depends on the ability to demonstrate a primary pulmonary disease which would affect the pulmonary vascular bed.

DR. KOSSMANN: Dr. Galdston was kind enough to come this evening to tell us about the pulmonary functional studies he did on this patient in the last months of his life at Goldwater Memorial Hospital.

DR. GALDSTON: Before the administration of adrenocorticotropic hormone the patient exhibited a borderline normal total lung volume (table 2). The vital capacity was reduced. There was an abnormally large absolute and relative volume of residual air. These are common findings with pulmonary emphysema. The excellent maximal breathing capacity indicated that bronchiolar obstruction did not contribute to the emphysema.

The minute volume of respiration was greatly increased even when the patient was afebrile and when his resting rate of oxygen consumption was within the predicted range. These data, together with a normal gas exchange ratio (R.Q.) indicate that the hyperventilation was the result of physiologic and metabolic drives. The volume of each breath which did not partake in gas exchange, the dead space, was abnormally large. One might expect an alveolar oxygen tension of less than 90 mm. Hg and a greater degree of carbon dioxide tension in the alveolar air than 48 mm. Hg with such maldistribution of gas in the lungs. The increased minute volume of ventilation most likely accounted for the minimal derangements in the tension of these gases. The results of the simultaneously measured oxygen tensions of alveolar air and of arterial blood when breathing room air (21 per cent oxygen) and again when breathing 30 per cent oxygen indicate that there were many poorly ventilated alveoli with capillaries well circulated with mixed venous blood. Exchange of oxygen was poor in these areas which may be considered to be veno-arterial oxygen shunts. The data also suggest, though they do not permit definitive quantitation, that impediments to oxygen diffusion, such as thickened alveolar-capillary membranes or absolute reduction in the effective gas diffusing surface, contributed to the oxygen unsaturation of the arterial blood. The further fall in arterial blood oxygen saturation and rise in pCO_2 of the alveolar air during moderate exercise are commonly seen in chronic pulmonary disease complicated by pulmonary hypertension. In short the patient exhibited many derangements in pulmonary function compatible with advanced emphysema and fibrosis.

During the period of therapy with adrenocorticotropic hormone some noteworthy improvements in pulmonary function were observed. The distribution of air to the alveoli improved as did the transfer of gas across the alveolar capillary membrane. These were manifested by a decrease in the ratio of dead space to tidal air, a rise in pO_2 and a fall in pCO_2 of the alveolar air, and an increase in resting arterial blood oxygen saturation.

The complications which occurred after discontinuance of adrenocorticotropic hormone permitted only a limited number of studies. These indicated, in general, a regression of pulmonary function to pretreatment levels.

CLINICAL CLERK: Can it be stated when this patient's heart disease began?

DR. BERGER: That question is difficult to answer because the stages of chronic cor pulmonale, which he was suspected of having, run

imperceptibly one into the other. Arbitrarily there is the precardiac phase, when pulmonary symptoms dominate; the cardiac phase without failure, when right ventricular hypertrophy is recognizable; and the cardiac phase with failure, which is the time when evidence of congestion behind the right ventricle begins to appear.

It was difficult to say just when this patient began to have failure of the right ventricle, and indeed there was, at times, a question whether there was any at all. The old lymphedema, present for 20 years, did not make the task easier. Obesity made palpation of the liver uncertain. There was x-ray evidence of enlargement of the right ventricle in 1949 when he was 60 years old. It was soon thereafter that symptoms were intensified. Sometime in 1950, the electrocardiogram began to show inversion of T waves in leads from the right side of the precordium. Actually distinct pitting edema and a palpable liver were regularly observed only in the last year of life.

Weighing all the facts it is probable that the clinical picture was dominated most of the time by the pulmonary dysfunction, and failure of the right ventricle was probably present for not much more than two years before death.

DR. KOSSMANN: The electrocardiograms, especially during the first three years of observation, were disturbing because they displayed left deviation of the electrical axis of QRS with an angle alpha of approximately +6 degrees with a normal ventricular gradient. Although we knew the patient had pulmonary disease, a normal blood pressure, a loud pulmonic second sound, latent hypertension in the pulmonary artery, normal cardiac output, polycythemia, clubbing, and minimal enlargement of the heart, it still was not certain, because of the persistent rales in the lungs, whether the evidences of congestion seen behind the right ventricle were from right ventricular disease, per se, or from combined left ventricular and right ventricular disease. Under these circumstances the electrocardiogram was not helpful until certain changes became manifest in the last year of life. Would you discuss the electrocardiograms for us, Dr. Rader?

DR. RADER: Five of the records made between Dec. 4, 1948 and Oct. 4, 1951 are shown in the chart (fig. 1). Others were available, and when precordial leads V_2, V_4, and V_6 were made, each usually resembled the precordial lead just to the right of it. A record with six chest leads made on Dec. 19, 1951 resembled the last one in the chart (Oct. 4, 1951). In it the T wave was inverted in the first three precordial leads, upright in the others.

A review of the records indicates that they were relatively constant between Dec. 4, 1948 and March 11, 1950. Beginning in 1951 the essential changes consisted of an increase in size of the T waves, and a change in direction of the spatial vector of T of such nature as to cause deepening of the T wave in lead III, and inversion in lead V_1. There also was some shift of the transitional zone of QRS to the left. In the record of Oct. 4, 1951, and in subsequent records (not shown) these trends were more marked, with the T wave inverted as far to the left as lead V_4, and further shift of the transitional zone of QRS to the left so that the R/S ratio was inverted in lead V_5. The T wave became inverted in lead aV_F. In terms of the spatial vector of the T deflection, it had rotated backward in a counterclockwise direction viewed from above, and upward.

There were, then, some modifications, beginning in January 1951, to suggest a considerable lengthening of the duration of the excited state on the right side and front of the heart such as is often seen more acutely when the pressure is raised in the right ventricle as in acute cor pulmonale. The shift of the transitional zone of QRS probably was the result of gradual dilatation of the right ventricle. To be noted is that there was no important change in the time of the intrinsicoid deflections in leads V_1 and V_3.

On February 15, five days before death, the electrocardiogram underwent a striking change: It showed, for the only time, a right deviation of the axis of QRS. The QRS interval was not widened, and the deflections in lead V_1 had the low W-shaped appearance often seen with right ventricular hypertrophy. It was suspected that the patient had a pulmonary embolus that day. In addition, the serum potassium was 8.3 mEq. per liter. On the next two days the record resumed its original appearance and axis of QRS,

although the voltage of the QRS deflections was low.

In retrospect perhaps too much attention was paid to the direction of the QRS deflections, and perhaps not enough to the T deflections, especially the gradual inversion over a period of time in leads from the right side of the precordium.

DR. KOSSMANN: Mr. Lehrer, what was the final diagnosis we made?

MR. LEHRER: The diagnoses made were: (1) Cardiac, (*a*) pulmonary arterial hypertension and arteriosclerosis, (*b*) enlarged heart, arteriosclerosis of aorta, (*c*) normal sinus rhythm, (*d*) IVE; (2) Pulmonary fibrosis and emphysema; (3) Hiatus hernia; (4) Anomaly of arteries to left arm; (5) Syphilis, late latent, Wassermann negative; (6) Possible chronic cholecystitis.

DR. KOSSMANN: If there are no other points let us go on to the pathologic findings.

PATHOLOGIST: The necropsy was performed 13 hours after death at Goldwater Memorial Hospital by Doctors Rosenkrantz and Vrbanovic. The significant findings were as follows:

The heart: weight 450 Gm., moderate hypertrophy of the right ventricle, none of the left (width of left ventricular wall 1.5 cm.); some sclerosis of the coronary vessels with considerable narrowing and calcification of the anterior descending branch of the left coronary; slight atheromatosis of the aorta.

The lungs: weight, right 1100 Gm., left 1000 Gm.; obliteration of the right pleural cavity; numerous small emphysematous blebs over the surface of the right lung, with larger blebs and bullae in the left upper lobe. The bronchi and bronchioles were dilated, and showed evidence of inflammation and proliferation. Sections of the lungs were firm, showed gross streaks of fibrosis, confirmed by microscopic examination. The pulmonary arteries showed moderate to advanced arteriosclerosis, and one large one displayed a recent thrombus with early organization.

The only other significant findings were congestion particularly of the liver (weight 1600 Gm.) which had a characteristic "nutmeg" appearance, and of the spleen (weight 250 Gm.).

PHYSICIAN: Was there any disease of the extrahepatic biliary tract or of the gastrointestinal tract?

PATHOLOGIST: Both were free of disease.

DR. KOSSMANN: It is evident from the postmortem findings that this patient had heavy, fibrotic lungs, predominantly right ventricular disease, and arteriosclerosis of the pulmonary arteries and arterioles. The latter finding is anatomic evidence of prolonged hypertension in that circuit. The stenotic coronary artery described may have been responsible for the subxiphoid pain. Before discussing the electrocardiograms in relation to the morbid anatomy, I believe it would facilitate matters to consider the contrasting case. Mr. Nash, will you proceed with the story of the second man's life?

CLINICAL CLERK NASH: F. A., a 52 year old male Puerto Rican elevator operator, was admitted to Bellevue Hospital on Oct. 25, 1951, because of increasing cough, dyspnea, orthopnea, fatigue, anorexia, and insomnia of three days duration.

The patient's symptoms began in 1950 when he was at another hospital for nonproductive cough, dyspnea, orthopnea and fatigue. He was told he had hypertension, was digitalized, and placed on a low salt diet. He remained on digitalis from that point on.

He had tonsillitis in 1934 and subsequently a tonsillectomy was performed. He had pleurisy in 1939 but denied pneumonia or respiratory sequelae. He never worked in an occupation where dust was a problem. An appendectomy was performed in April 1951. The patient was born in Puerto Rico, moved to the U. S. in 1920, and returned to Puerto Rico for a month in 1931; there was no other travel.

The family history was noncontributory.

Examination on admission on Oct. 25, 1951, revealed a poorly developed, dyspneic male, 64 inches tall, weighing 105 pounds, and appearing older than his stated age. Positive findings included: A diffuse maculopapular rash on the trunk; questionable hyper-resonance of the lungs; medium moist inspiratory rales posteriorly on both sides below T10. The point of maximal impulse of the heart was felt in the sixth intercostal space at the anterior axillary line. There were no thrills or murmurs. The pulmonic second sound was louder than the aortic second. There were a few premature systoles. An apical gallop rhythm was present on admission, but disappeared later. The blood pressure was 190/118 mm. Hg. There were no signs of congestion of the abdominal viscera although the cervical veins were distended. There was retinal arteriolarsclerosis.

There was 2 plus or more proteinuria on repeated urinalyses, although the specific gravity varied from 1.004 to 1.022 on a concentration and dilution test. The blood count was normal as was a Mazzini test.

The blood non-protein nitrogen was 45 mg. per 100 ml. The venous pressure was 112 mm. H_2O; the circulation times were ether 15 seconds, decholin 28 sec.

X-rays (fig. 3) displayed a vertical heart with an increase in the transverse diameter. On fluoroscopy the enlargement was principally to the left with enlargement of the inflow and outflow tracts of the left ventricle. The left border was straight, although the pulmonary artery was not enlarged. With barium swallow there was some displacement of the esophagus posteriorly by an enlarged left atrium (fig. 3).

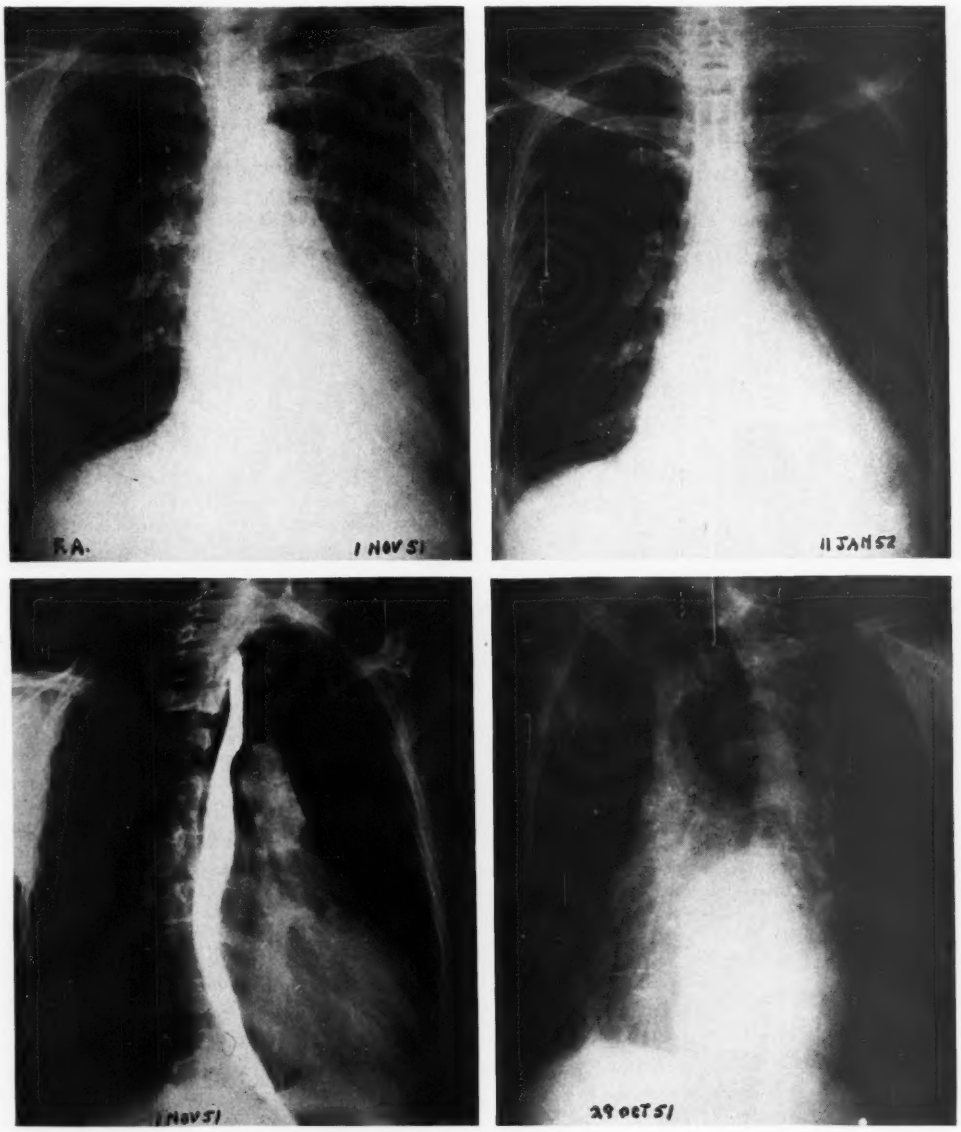

FIG. 3. Patient F. A. Teleroentgenograms with right anterior oblique (lower left) and left anterior oblique (lower right) views made on dates indicated. In the x-ray of Jan. 11, 1952, a patch of consolidation can be seen near the right costophrenic sulcus.

Pulmonary function studies are summarized in table 3. The significant changes were in the vital, total, and maximum breathing capacities which were reduced. The absolute residual volume was normal but the relative residual volume increased. The

TABLE 3.—*Studies of Pulmonary Function of Patient F.A. Made on Nov. 3, 1951*

	Observed Value	Predicted Normal Value	Per Cent Deviation
A. Lung Volumes (Supine Position in cc., BTPS)			
Respiratory rate	28	16	
Tidal volume	491	500	−1.9
Inspiratory reserve	1,384		
Inspiratory capacity	1,875		
Expiratory reserve	849		
Vital capacity (VC)	2,660	3,560	−25.2
Functional residual capacity (Exp. Res. + RV)	2,513		
Residual volume (RV)	1,664	1,590	+5
Total capacity (TC) (VC + RV)	4,324	5,150	−16
$\frac{RV}{TC} \times 100$	38.5	30.8	+25
Index of pulmonary mixing	.92	After breathing 100% O_2 for 7 minutes there is normally no more than 2.5% N_2 left in the alveoli.	
B. Maximal Breathing Capacity (MBC)—Standing Breathing Reserve (BR)		in Liters/min., BTPS	
Maximal breathing capacity (MBC)	71.5	87.1	−18
Minute volume (MV)	13.75	9	+53
Breathing reserve (BR) (MBC-MV)	57.75	78.1	−26
$\frac{BR}{MBC} \times 100$ = Dyspneic index	81	89.7 When this ratio is 70% or less dyspnea is generally present.	−9.5

minute volume was also increased. The arterial pO_2 was 91.5 mm. Hg, pCO_2 38.65 mm. Hg, and oxygen saturation 96 per cent. The findings were interpreted as being compatible with left ventricular failure without intrinsic pulmonary disease.

The electrocardiograms, with one exception, displayed a normal sinus rhythm or sinus tachycardia with right axis deviation and low voltage of QRS (fig. 4).

Therapy consisted of digitalis 0.1 and 0.2 Gm. on alternate days, a salt free diet, and bed rest. He improved gradually and became less dyspneic. However, medium rales persisted at both bases. After 20 days he was discharged to the Adult Cardiac Clinic with the diagnosis: Cardiac (*a*) hypertension, (*b*) enlarged heart, (*c*) normal sinus rhythm, (*d*) class IIIC. Accompanying condition: pulmonary fibrosis and emphysema.

He was seen in the clinic three times in as many weeks, each time complaining of cough, dyspnea, orthopnea and insomnia. The physical findings were as previously with the additions of 3 plus ankle edema, and a liver edge palpable 2.0 cm. below the costal margin. The apical gallop reappeared. Digitalis was increased to 0.2 Gm. once daily, but he became toxic after five days. He stopped the drug for three days and resumed the day before his last clinic visit on Dec. 20, 1951. In view of the problem of digitalis toxicity and continued heart failure, the patient was readmitted to the hospital that night.

In the hospital the second time the course was irregularly febrile and downhill with increasing and intractable edema. There was a moderate leukocytosis with a persistent shift of the index to the left. The blood nonprotein nitrogen gradually rose from 59 to 100 mg. per 100 ml. Dullness was noted over both lower lobes. A few days before death a thick, tenacious, bloody material was found in the mouth, but there was no frank hemoptysis. The clinical impression was bronchopneumonia. A culture of the sputum grew out gram positive diplococci.

Despite antibiotics, oxygen, mercurial diuretics, and the usual supportive therapy, tachypnea was progressive, the blood pressure fell to 110/94 on January 21, and the patient died the following day in heart failure.

DR. KOSSMANN: The problem presented by the second case is a little different from the first. He was about the same height as the first patient but weighed only 100 pounds. He displayed in life definite left ventricular disease and heart failure, and peripheral sclerosis, but also showed questionable hyper-resonance of the lungs, a cough, a pulmonic second sound louder than the aortic, pulmonary functional tests revealing moderate dysfunction, and an electrocardiogram showing with one exception (fig. 4) right deviation of the electrical axis of QRS. Dr. Rader, would you discuss the electrocardiographic data further?

DR. RADER: Between Oct. 26, 1951 and Jan. 22, 1952, 10 electrocardiograms were recorded. The patient was receiving digitalis the entire

time. Four of these are shown in figure 4. All but the second record (fig. 4, first line, Oct. 31, 1951) showed distinct right deviation of the electrical axis of QRS (angle alpha approximately +120 degrees) and left deviation of the electrical axis of the T wave such as is often seen in patients with advanced hypertrophy of the right ventricle. Further, there were high, pointed P waves in leads II and III, and a prominent diphasic P wave in lead V_1

The precordial leads show prominent S waves far to the left except in the first record, but no late intrinsicoid deflections in lead V_1. Interesting, too, is the absence of a late R wave either in lead aV_F or lead aV_R, although a notch on the descending limb of the R wave of lead aV_F in the records of Dec. 21, 1951 and Jan. 11, 1952 is fairly late (between 0.05 and 0.06 second from the beginning of QRS in that lead). Lead V_6 (not shown) usually

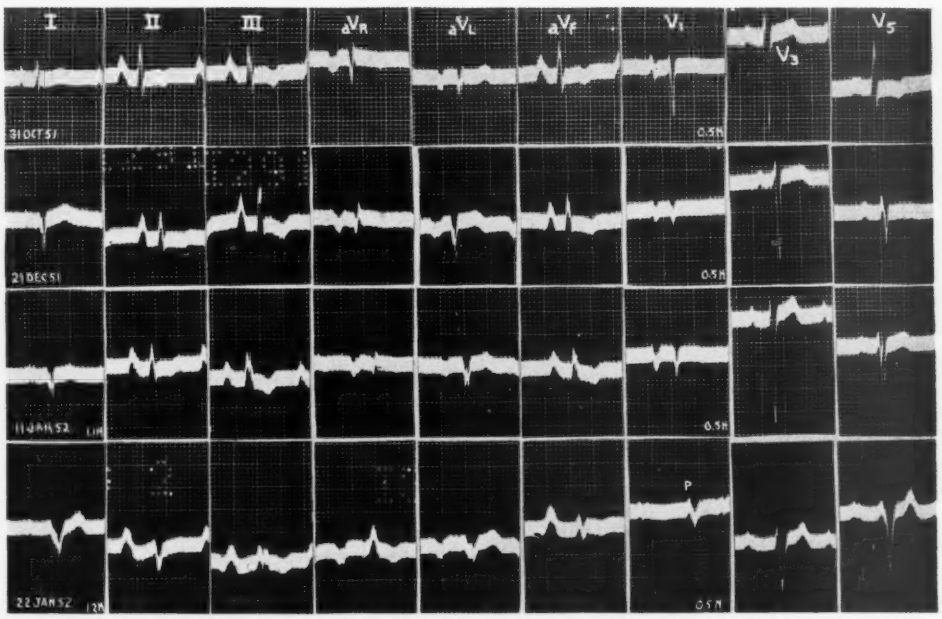

FIG. 4. Patient F. A. Electrocardiograms made during the last three months of life on dates indicated. The symbols have the usual meaning; the precordial leads were recorded with the sensitivity reduced to one half (1 mv.=0.5 cm.). The last record (Jan. 22, 1952) was made on the day of death, and discloses widespread defects of conductivity.

In the record of Dec. 21, 1951, the P wave in lead III is higher than in leads I and II because there was some shifting of the pacemaker.

such as is sometimes seen in chronic cor pulmonale, but more often in acute cor pulmonale. The ventricular gradient was probably not abnormal until the last record (Jan. 22, 1952). The latter, made three hours before death, shows a considerable increase in the intra-atrial, atrioventricular, and intraventicular conduction times. Since the patient was tachypneic with azotemia not much can be said of the significance of this record in terms of the anatomic alterations encountered at necropsy.

looked like V_5 in the upper record (Oct. 31, 1951) with an inverted T wave. The R wave in it was early (0.03 second).

DR. KOSSMANN: The course of this patient's heart disease was less than two years from the time he first developed manifestations of diminished cardiac reserve until death. In that period, nine months before his death, he was able to go through an appendectomy. With the exception of the terminal state, the blood pressure remained elevated with the diastolic never below

110 mm. Hg. The data on the mildly impaired pulmonary function gave no exact indication of the possible anatomical cause. What was the final diagnosis we made in the clinic?

MR. NASH: (1) Cardiac: (*a*) hypertension, arteriosclerosis, and unknown, (*b*) enlarged heart, coronary sclerosis, myocardial fibrosis, (*c*) normal sinus rhythm, gallop rhythm, congestive heart failure, (*d*) class IVE; (2) pulmonary fibrosis and emphysema.

DR. KOSSMANN: It is obvious that something further occurred in the lungs just before death. If there are no questions on the clinical data we will go on to the pathologic findings.

PATHOLOGIST: The necropsy was performed on Jan. 22, 1952, by Drs. David Schwartz and Norman Cooper. The examination of the brain was done by Dr. L. D. Stevenson. The essential findings were as follows:

The heart: The heart weighed 525 Gm. All chambers were markedly dilated. The left atrial appendage contained a small thrombus. There were several small thrombi, the largest 1.0 by 0.5 by 0.2 cm., between the columnae carneae of the apical region of the right ventricle. The left ventricle contained a larger number of thrombi, similarly distributed. The largest of these, 3 by 2 by 3 cm., was in the posterior apical area of the left ventricle. Small areas of gray-yellowish discoloration of the myocardium were found under this thrombus. There were no areas of myocardial softening or hemorrhage, and the myocardium in general was red-brown. The major coronary arteries were patent and had a moderate amount of atherosclerosis. There were foci of marked constriction in the left circumflex artery. The foramen ovale and ductus arteriosis were obliterated. The left ventricular wall was 1.9 cm. thick, the right 2 mm. The valve ring circumferences were: tricuspid 13 cm.; pulmonic 8 cm.; mitral 10 cm.; aortic 7 cm.

Great vessels: There was a relatively small amount of atherosclerosis through the course of the aorta. There was a moderate reduction of its elasticity. The inferior vena cava, portal vein and iliac veins appeared normal.

Lungs: The left lung weighed 300 Gm., the right 250 Gm. There was no fluid in the pleural cavities. The pleural surfaces were smooth and shiny. There were small bilateral apical pleural scars. A major part of the right lower lobe was hard and dark blue. Its cut surface was dark red, shiny, and roughly wedge-shaped. It was moderately well demarcated from adjacent tissue; small interspersed uninvolved areas made it evident that the lesion was multiple. There was a 2 by 2 cm. similar area in the left lower lobe, and small areas in the right upper lobe and left lower lobe; some of these were paler gray-red. The major artery to the right lower lobe contained a thrombus which did not conform to its shape. Small arteries in all lobes contained thrombi and propagated thrombi. The bronchi were normal. Uninfarcted pulmonary parenchyma was congested posteriorly, normal anteriorly.

Microscopic sections revealed moderate hypertrophy of the myocardial cells, but, in addition, an inordinately large amount of interstitial fibrosis. Most myocardial fibers were surrounded by thin laminae of reticulum or denser collagen. There were some areas of replacement by scar tissue. The thrombus in the left ventricle was undergoing organization but not the one in the left atrium.

Sections of the lungs confirmed the gross impression of infarcts.

Other significant findings included: Chronic passive congestion of the liver and pancreas; thrombosis of the periprostatic veins; arteriolar hyalinization and thickening in the spleen, pancreas, adrenals, kidneys, and brain.

In summary, the heart displayed evidence of dilatation, and predominantly of left ventricular hypertrophy. Although there was coronary stenosis, it did not cause myocardial infarction, and the degree of interstitial fibrosis and the intracardiac thrombi could not be accounted for on the basis of the coronary disease alone. There were stigmata of systemic hypertension and of prolonged cardiac insufficiency.

DR. KOSSMANN: Any questions?

CLINICAL CLERK: Is there no explanation at all for the myocardial fibrosis and mural thrombi?

DR. BERGER: Apparently the pathologist was impressed with the paucity of coronary disease to account for these findings. If this patient did not have hypertension during life the patho-

logic findings would be reminiscent of several patients we have seen recently at necropsy. These patients showed hypertrophy, mural thrombi, variable amounts of myocardial fibrosis, and little or no coronary disease. In some instances these findings were probably the end result of repeated bouts of failure on the basis of thiamin deficiency such as seen in chronic alcoholism. However, in some they occurred in the absence of vitamin deficiency. Clinically the dominant picture is one of heart failure, and the patients usually are classified as having "unknown" heart disease. It seems that with refinements in clinical technics we are making this etiologic diagnosis of "unknown" more often. This fact points up the considerable limitation in our knowledge at present about the real causes of impaired contractility of the myocardial cell.

This patient was unusual in that he had hypertension during life sufficient to cause hypertrophy of his heart, but in addition showed an unaccountably large amount of myocardial fibrosis.

DR. KOSSMANN: We are now ready to attempt an over-all summary and an explanation of the atypical electrocardiograms in the light of the anatomic alterations found at necropsy.

These two men happened to be approximately the same height but one was fat and one was lean. Each presented himself with signs and symptoms referable to dysfunction either of the heart or of the lungs. Clinically, at least, symptoms from the latter organ dominated in the fat man; symptoms from the former dominated in the thin man. The pulmonary functional studies bore out the clinical impression, and hemodynamic studies in the first patient gave a very good suspicion of primary pulmonary disease as the cause for pulmonary arterial hypertension.

The laboratory data which did not fit with the others were the electrocardiograms. The man with proven right ventricular hypertrophy displayed deviation of the electrical axis of QRS to the left; the man with proven left ventricular hypertrophy displayed deviation of the electrical axis of QRS to the right.

The electrophysiologic reasons are clear enough from an inspection of the records (figs. 1 and 4). In the fat man the potential of the left arm (aV_L) was positive with respect to the potential of the left leg (aV_F). Originally, Einthoven made connections between the body and the galvanometer in such a way that with a potential of these two extremities as indicated, a record of the difference between them (lead III) would display a downward deflection. In lead III there was a deep S wave (fig. 1) indicating a mean direction of excitation of the heart with respect to that lead from below upward. In so far as excitation was from right to left in lead I, as can be seen from an inspection of this lead and the potential of its component extremities, the mean electrical axis was "deviated to the left." In the thin man the situation was reversed with the potential of the left leg and of the right arm (with one exception) more positive than of the left arm. This electrical situation resulted in "right deviation" of the electrical axis in the frontal plane.

It is worth noting that the QRS deflections in the precordial leads (figs. 1 and 4) of the two patients were not too dissimilar. This would seem to indicate that the important differences in ventricular excitation between the two were in the frontal plane, but not in the sagittal plane. One might go further, on the basis of known data,[3, 4] and strongly suspect that the differences noted in the two records depended not so much on the relative size of the right and left ventricles in each case but rather on the different relationships each of these chambers bore to the left arm and left leg in the two men. This is equivalent to saying that hypertrophy had little to do with the mean direction of ventricular depolarization except in so far as it determined the position of the heart in two patients with widely different thoracic configurations. Further, the combinations—short, round thorax with right ventricular hypertrophy; long, flat thorax with left ventricular hypertrophy—were of such nature that in each instance position of the chambers with respect to the extremities used for leading in the frontal plane far outweighed the effect of any preponderance[5] caused by hypertrophy of one or the other ventricle.

It was pointed out that the T waves gradually underwent inversion in leads from the

right side of the precordium in the patient with chronic cor pulmonale. This alteration, if it occurs with any great frequency in this disease, is probably of considerable diagnostic value, and certainly was not properly evaluated in this instance. Of interest, too, is the fact that the transitional zone of QRS was shifted to the left in both patients.

This brings us back to the matter of "incidence" mentioned at the beginning of the conference. Probably less—and our own observations indicate considerably less—than 70 per cent of patients with right or left ventricular hypertrophy will show the electrocardiographic configuration "characteristic" for the chamber involved. Correlations in general will be better the greater the hypertrophy.[6] Under the circumstances it is almost incorrect to speak of the configuration as "characteristic." Certainly to do so leads to error; and error is especially common if the electrocardiogram has a contour usually associated with hypertrophy of the contralateral ventricle, as was true in these two patients.

In conclusion, I would say that, in addition to others, the points learned here were: (1) A knowledge of incidence of a phenomenon in a disease, though helpful, must be properly evaluated before being used in an absolute way; (2) it is unsound practice to make final anatomic cardiac diagnoses from the form of the electrocardiogram without recourse to other clinical and laboratory data.

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CLINICAL PROGRESS

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The Patient with Cardiovascular Disease and Rehabilitation: The Third Phase of Medical Care

BY JOSEPH G. BENTON, PH.D., M.D. AND HOWARD A. RUSK, M.D.

ONE of the most striking developments in recent medical thinking has been the evolution of the philosophy of rehabilitation, or the "third phase of medical care." The impact of this discipline on medical practice stems from the widespread intensification in contemporary medical teaching of the concept which delineates "the patient as a whole"—his relationship not only to himself, to his family, and to his work, but to the total community.

Development of rehabilitation programs has been paradoxically furthered by the recent advances made in the control of infectious diseases as well as in improved surgical and public health technics which have extended the life span in this country. As a result, greater numbers of the population will fall into the category of patients with chronic disease. While it is probable that current investigational activities will eventually clarify the etiologic bases and methods of prevention of such entities as arteriosclerosis, hypertension, degenerative neurologic disease and cancer, there is a critical need for salvaging the large numbers of individuals with the residua of chronic disabling disease who now constitute serious medical and social problems. This has significant implications for the patient as well as the community at large.

Rehabilitation was defined at the first (1950) National Conference on Cardiovascular Diseases as "the return of a person disabled by accident or disease to his greatest physical, mental, emotional, social, vocational, and economic usefulness, and, if employable, an opportunity for gainful employment." In addition, it was emphasized that "it should not be confined to economic or vocational rehabilitation but should aim at the maintenance of the personal dignity of the individual and the expansion of his capacity for living by enabling him to make the best of his physical and mental faculties." Rehabilitation, therefore, carries the patient from "the bed to the job."

The relationship of rehabilitation to the patient with cardiovascular disease in its broadest sense is evident. The need for such programs in the disease entity which is first in mortality incidence and high in morbidity with resultant undetermined economic loss becomes clear. In this connection, it is to be noted that industrial absenteeism as the result of cardiovascular disease in the first half of 1952 was preceded in incidence only by respiratory diseases.[1] The need is further demonstrated by the number of patients discharged with diagnoses of cardiovascular disease or its complications from the various services of this Department in 1950; they numbered 158 (49 per cent) of a total of 325 discharges with diagnoses of nontraumatic disease. In addition, there were 151 discharges

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Original studies reported herein were supported in part by grants from the Milbank Memorial Fund and the National Heart Institute, United States Public Health Service (H-790 and C-1 and 2).

on a traumatic (industrial, traffic, etc.) etiologic basis, making a total discharge number of 476 of which the cardiovascular disease groups comprised 33 per cent. Of the latter, 90 per cent had significant underlying systemic disease which necessitated regulation of the cardiac therapeutic regimen in accordance with the progressive demands of the graduated retraining program.

Rehabilitation in some medical circles has unfortunately assumed a "catch word" connotation. This, at once both the oldest and the newest of the medical disciplines, proposes to effect no miracles but rather attempts to assess and manage the patient from sound bases of medical, physical and occupational therapeutic, speech and hearing, prosthetic, psychiatric, vocational counseling, prevocational training, social service, and therapeutic recreational programs. This implies and actually epitomizes in its most cogent fashion the "team approach." It must be strongly emphasized that the leading and cohesive influence must be exerted by the physician, since the basic problem concerns a patient with a disease process. There has been recent consideration of rehabilitation in some quarters as a "paramedical" discipline. Nothing could be further from the truth; nor can it be considered as "glorified social work." Medical rehabilitation has a primary medical basis, and, as a result, the guiding force remains the physician. A rehabilitation program can only be effective if candidates for retraining are properly selected. It is a general principle that patients in whom the underlying disease process progresses at a more rapid rate than the retraining process are not feasible for such programs. Only the physician can determine this. In addition, observation of the patient in terms of cardiac reserve is necessary during the retraining process, particularly during ambulation and exercise phases. This is especially true of the patient with cardiovascular disease.

In rehabilitation, disability of patients with cardiovascular disease may be considered as comprising two main categories: (*A*) that which results from a complication of underlying systemic cardiovascular disease where the disability is "overt," for example, hemiplegia as the result of a cerebrovascular accident, and (*B*) that which results from diminished cardiac reserve and which appears in the form of signs and symptoms of cardiac decompensation as the result of activity, either of daily living or occupational. This may be considered as "masked" disability.

A. The First Category

Hemiplegia is most frequently due to cerebrovascular thrombosis, followed next in order of frequency by hemorrhage and embolism. Etiologically, in decreasing incidence, it occurs in arteriosclerosis, hypertension, rheumatic or congenital cardiovascular disease. It has been estimated that there are at present in this country approximately a million patients with hemiplegia with varying degrees of disability. As previously indicated, a large percentage of such patients observed on the services of this Department have a degree of underlying systemic cardiovascular disease which requires management in terms of variations in digitalis, diuretic and other therapy to allow for effective participation in the retraining program.

In addition, since mitral valve commissurotomy and other cardiac surgical procedures will become more widely performed, it is anticipated that hemiplegia resulting from the occasional postoperative complication of cerebral embolism will increase the number of potential candidates for rehabilitation training. Three such patients have come under observation in this Department this past year. These were all highly motivated and relatively young individuals with important vocational and household responsibilities. This type of patient makes an excellent candidate for retraining. Clinical observation during the ambulation program indicates that these patients maintained adequate cardiac reserve postoperatively for effective and safe participation in the retraining program.

The early management of the acute cerebrovascular episode primarily involves purely medical and possibly surgical considerations where indicated. Measures in the acute phase are supportive and prophylactic. The efficacy of stellate ganglion block is dubious. A recent controlled study[2] has indicated that there was no significant effect of this procedure on hemi-

plegia. Such studies are needed to clarify this problem since the technic is not wholly innocuous and is apparently widespread in its application. Further understanding of the physiology of the cerebral circulation in man with reference to autonomic nervous system function and other homeostatic mechanisms is required in this respect. Development of the nitrous oxide technic[3, 4] has allowed quantitative observations of cerebral hemodynamics and metabolism as effected by stellate ganglion block,[5, 6] a variety of drugs, [7-11] and in certain disease states.[12] In addition, a recent report[13] indicates that at a level of exercise of energy cost three times the basal level, cerebral blood flow in normal subjects was significantly increased.

Since it has been suggested that there is a tendency for cerebral vascular episodes to be repetitive, it would appear worthwhile to explore the value of anticoagulant therapy with long range follow-up in a series of such patients, properly selected and excluding those with hemorrhage. To date no study of this nature, adequately controlled, has as yet been reported. With stabilization after the initial insult, management involves graduated sequences of active and passive motion of the affected extremities, ambulation, and speech training if aphasia has supervened. Objectives of early management are the prevention of contractures and deformities. Rehabilitation procedures can begin as soon as the patient regains consciousness when it is relatively certain that thrombosis has occurred. The same applies where hemorrhage is suspected, but here only careful passive procedures, carried out in bed, should be allowed for a period of three weeks. Where the etiologic factor is embolism, active rehabilitation procedures may be started with the return of consciousness if no other systemic contraindication exists.

As already indicated, retraining is not considered feasible where the underlying pathologic process progresses at a more rapid rate than the rehabilitation program. For this reason, the question of case selection is of special importance with reference to cardiovascular disease. Patients in the malignant phase of arteriolonephrosclerosis, with involvement of cerebral cortical tissue to such an extent as to preclude adequate mentation and retention, and intractable coronary insufficiency or congestive failure are not suitable candidates for undertaking such programs.

The various steps in rehabilitation of the patient with hemiplegia involve a graduated sequence of procedures which carry the patient from the bed through ambulation and activities of daily living which make for self sufficiency and, if feasible, in selected instances through vocational retraining and eventual job placement. Such patients can be evaluated and followed objectively by the use of charts for muscle strength (Brünstromm modification of Lovett method), range of motion (goniometrically determined), and activities of daily living (ADL) for serial analyses before, during, and after such training programs. Using these methods in a carefully controlled study and quantitating the results, it has been shown[14, 15] that a group of patients who had undergone rehabilitation demonstrated an increment of more than 130 per cent in activities of daily living when compared with a control group that had no rehabilitation training. Both series of patients were selected with regard to age, sex, etiology, type of cerebrovascular accident, and especially with regard to time after the acute insult. In addition to the increment in activities of daily living, increases were also noted in range of motion and muscle strength in the retrained group.

The general details of such a rehabilitation program are as follows:

I. Procedures which are started while patient is in bed

1. A foot board or posterior leg splint to prevent foot drop.

2. Sand bags to prevent outward rotation of the affected leg.

3. A pillow in the axilla of the involved upper extremity to minimize adduction and internal rotation.

4. Quadriceps muscle setting of the involved lower extremity to maintain muscle strength.

5. Sitting in bed to help re-establish balance. (This may at first be assistive, but later the

patient may use a sheet tied to the foot of the bed as an aid in doing this himself.)

6. Speech therapy if the patient is aphasic (where the insult occurs in the dominant hemisphere). This may be done by a speech pathologist, or if not available, by a speech or elocution teacher who often can be recruited from local high schools, or colleges. In this connection, it has been our experience that the prognosis for return of speech is more favorable if the aphasia is of the expressive type. This aspect of retraining should be intensive, especially in individuals who have developed this avenue of communication to a high degree, since in these the speech difficulty is especially frustrating and often leads to significant psychologic overlays which interfere with the rehabilitation program.

7. Pulley therapy to prevent shoulder ankylosis and to aid in the development of reciprocal patterns in the upper extremities. This can easily be managed with the use of a modification of an overhead frame, a clothesline pulley, and a length of clothesline. (In addition, a member of the family or the attendant may be taught to give passive range of motion.) Experience has shown that relative return of function in the affected arm is usually less than in the involved leg. The reason for this is still obscure. Accordingly, emphasis should be placed as early as possible on the use of the unaffected arm; this is especially true of the relatively young patient with rheumatic heart disease. In addition, a triangular arm sling should be used to elevate the affected arm. This is of some aid in minimizing localized edema which frequently supervenes in the extremity.

II. Procedures which are initiated when patient is out of bed

1. When ambulation is started, the patient (*a*) practices balancing in the standing position; (*b*) uses parallel bars (two ladderback kitchen chairs on a smooth wood or linoleum surface may be substituted); (*c*) is taught heel and toe gait to prevent clonus and to re-establish normal walking habits; (*d*) stresses reciprocal motion in both the upper and lower extremities; (*e*) uses a short leg brace to correct foot drop (approximately half of cases). In those individuals where the quadriceps muscle of the involved extremity remains poor or at zero level of function, a long leg brace should be considered, with the possibility of an ischial weight-bearing attachment.

2. While ambulation is continuing, the patient is taught how to manage stairs, ramps, and how to enter an automobile or bus.

3. Activities of daily living are also taught. These include: (*a*) personal care; (*b*) feeding; and (*c*) hand activities such as opening doors, operating light switches, and telephone dialing. As aids in these activities, modifications of standard implements have been devised such as a knife (serrated cutting edge) and fork on one handle, zippers instead of laces in shoes and zipper front shirts. For the hemiplegic housewife, slight modifications in the physical aspects of the kitchen can allow for effective functioning. The details of such a retraining program have been fully outlined in a recent monograph, which, in addition, considers other features of hemiplegia as a disease entity.[16]

After a satisfactory score in activities of daily living has been attained by the patient, aptitude testing, vocational retraining, if necessary, and selective placement may follow.

Results obtained with this dynamic approach indicate that the outlook for the hemiplegic patient is far from hopeless, provided intelligent case selection is effected. In our experience, approximately 92 per cent of such patients can be rehabilitated to the point of discharge from the hospital with self-sufficiency in activities of daily living in an average of from six to eight weeks, and roughly one-third of these can be placed effectively in selected vocational activities.

B. The Second Category

The second category of patient with cardiovascular disease for whom rehabilitation has great significance comprises those individuals with hypertensive, arteriosclerotic, syphilitic or rheumatic myocardial and valvular lesions whose cardiac reserve is so diminished that signs and symptoms of decompensation supervene during activity, either of daily living or of occupation. This group would also include

those with iatrogenic heart disease, who fear activity because they have been told by physicians that they suffer from heart disease and should therefore curtail or modify work habits —information often given without specificity. In this connection, it is to be noted that the Work Classification Unit at Bellevue Hospital has demonstrated[17] that of a total of 631 adequately studied patients 175 (28 per cent) did not have cardiac disease but had been carried as such for varying lengths of time. Many cardiac patients can work provided careful diagnosis is made, motivation is present, anxiety alleviated, adequate tolerance studies performed, and they are selectively placed in jobs whose demands are matched by their physical capacities. This has been demonstrated by the experiences of the War Manpower Commission, Eastman Kodak Company, Pratt and Whitney Aircraft Company, among others.

Probably the greatest deterrent to a quantitative approach to the problem of these patients has been the lack of objective methods of study within the rehabilitation framework. It is evident that accurate and meticulous diagnosis of the underlying cardiac condition is mandatory. Patients with aortic and mitral stenosis to any significant degree should not be considered for occupational activities in which the public safety might be endangered where sudden syncope may supervene unexpectedly (notably public transportation work, window cleaning, and other scaffolding jobs).

While there have been isolated observations reported of experiences relative to employment of cardiac patients, these have been from a comparatively restricted industrial medical point of view. However, the most carefully analyzed data are those reported by the Work Classification Unit established as a functional component of the Thursday Night Adult Cardiac Clinic of the Third (NYU) Medical Division at Bellevue Hospital in 1941; this was supported for a time by the New York Heart Association. This cooperative venture proved to be a prototype of the Work Classification Units which are now becoming established not only in other cardiac clinics in New York City but throughout the country. While the patient population (631) analyzed may not be truly representative, basic observations relative to etiology, duration of employability, effect of employment on cause of heart disease, absenteeism, and other relevant matters, have been made by this group. Emphasis by this Unit has been placed, as previously indicated, on the relatively high percentage (28 per cent) of patients who had been carried as "cardiacs" for a number of years with resultant interference in work patterns, and who, upon careful examination, were revealed not to have heart disease. It is possible that the source of patient referrals will condition figures such as these since only 5 per cent of a total of 250 patients surveyed by the Work Classification Unit in Cleveland, Ohio, were carried as cardiacs who, after careful evaluation, were found to be free from cardiac disease.[18] It is obvious from this that adequate diagnosis, in which all known technics are employed, should be the basis for any rehabilitation program.

The need, however, for an objective clinical measure of cardiac reserve in the patient with valvular or myocardial damage is great since the universally employed functional and therapeutic classifications of the Criteria Committee of the New York Heart Association, while subserving an extremely useful function, still depend considerably on the clinician's judgment and, furthermore, do not attempt actually to assess the patient's ability to do work of known energy cost. In addition, important psychological factors are difficult to estimate.

Laboratory technics involving cardiac catheterization are widely being utilized to study basic hemodynamics in normal as well as cardiac subjects. Such studies have resulted in clearer understanding of cardiovascular function and have had great influence in the development of the newer cardiac surgical technics. Patients with indwelling arterial and venous needles, or catheters, mouthpieces, or other similar appliances in place, who are lying on an x-ray table in a darkened room peopled by anywhere from four to six busy investigators and who are asked to pedal a bicycle at a cadenced rate, will hardly present a truly basal picture for purposes of job placement. While rises in pulmonary artery pressure measured by

means of the catheter may indicate the earliest sign of encroachment upon cardiac reserve, such methods are not feasible for routine clinical use for purposes of rehabilitation. To this end it would appear that the energy costs of specific standardized activities for the cardiac patient might be useful as a possible starting point. The assessment of actual work capacity may be very difficult to measure exactly, and can be dealt with indirectly by a knowledge of the approximate physiologic stress resulting from a given physical activity. This stress may be judged from the rate of energy cost required to accomplish the activity which may be of daily living or occupation. As far as is known there is no detailed information relative to this available, although a short abstract has indicated the energy cost of groups of cardiac subjects during three levels of bicycle ergometer exercise.[19] There is apparently no reference in the literature relative to energy cost of activities of daily living or occupation for the cardiac subject. There is some information for normal subjects relative to energy cost involved in standardized laboratory activities (bicycle and treadmill) in the American literature and for that involved in actual jobs in the lumbering and shipbuilding industries, as well as in laboratory bicycle exercises, in the Swedish literature. Studies of similar nature involving certain occupational activities with tuberculous patients as subjects have been reported.[20]

Housewives, who constitute the largest segment of the working cardiac population, have apparently been overlooked in programs of rehabilitation. As far as is known, there have been no energy cost studies reported for such patients. The need here is critical, since the woman with cardiac disease continues, of necessity in many instances, to do kitchen and housework. Such programs should consist of retraining as well as the development of energy conserving methods for the performance of routine household duties and design of household and kitchen equipment. To this end, a model kitchen, first assembled by the New York Heart Association, was made available to this Department for both patient training and research.

In view of the foregoing, studies of oxygen consumption, using both the closed respirometric, as well as the open (Douglas bag and Scholander gas analysis) technics in both normal subjects and cardiac patients under a variety of standardized activities, were undertaken. Oxygen consumption was calculated in milliliters per kilogram of body weight at normal temperature and pressure and referred to resting metabolic oxygen consumption. All subjects were carefully evaluated; hematologic, respiratory or endocrine dyscrasia which would have interfered with oxygen consumption precluded selection for study.

It has been demonstrated, for example, that both cardiac and noncardiac subjects expend less energy, as measured by oxygen consumption, in using the bedside commode for defecation than in using the bedpan.[21] For the use of the commode the energy cost was at a level of three times, while the use of the bedpan was at a level of four times the resting oxygen consumption. This difference was statistically analyzed and a p value of less than 0.001 (computed according to Fisher and Yates) derived, which indicates that the difference was highly significant. In addition, the cardiac patient and the normal subject did not significantly differ with regard to the energy cost for performance of these activities. These data would appear to substantiate by objective physiologic evidence the clinical impression of the deleterious effects of the use of the bedpan and would appear to add to the significance of the recently advocated "armchair" treatment of acute coronary thrombosis.[22]

Step walking on a staircase (six steps, each 7 inches high; total vertical height for one trip, 42 inches) was chosen as a basic task for exploration since this represents an activity requiring no learning or training and is one which is essential in the daily life of every individual employed outside the home who depends on public transportation to get to and from his place of employment. Inability to perform this important ambulatory function would place an almost insurmountable barrier in the path of occupational rehabilitation, particularly in the group of patients that come under observation in this Department.

In a series of over 50 cardiac subjects of all

etiologies and ranging in functional classification from I through III, the performance of level walking and graduated stair walking (round trip) activities under standardized conditions was at a level of energy cost as measured by oxygen consumption ranging from 6.6 to 72.5 ml. per kilogram of body weight (approximately 2 to 24 times above the resting metabolic rate).[23] Most of the cardiac patients, including those classified as III, could perform these activities without serious difficulty. All cardiac subjects observed in these studies were compensated and on adequate maintenance regimens. The results again compared very closely with those obtained with 44 noncardiac subjects.

The significance of these findings lies in the fact that very few actual working activities other than exceedingly heavy labor require a sustained output of more than two to four times the resting energy metabolism. It has been pointed out[24] that work may be considered moderate when its cost is three times that of the basal rate, and strenuous when the cost increases to eight times the basal rate. It might be postulated, therefore, that these patients have a good to excellent potentiality for work of moderate energy cost, other factors such as motivation and aptitude being equal.

Similar studies[25] have been performed in our occupational therapy shops for standardized activities involving the upper extremities and trunk musculature. These were designed to bring into function the major muscle groups. The subject was required to (1) cut a piece of pine board of standard dimensions into three outlined pieces by hand crosscut saw, (2) file and sand the cut edges and outside surfaces of the three pieces of wood, and (3) assemble the three pieces into a stool after boring holes with a hand drill and placing four screws by manual screw driver. These activities were designed for the purpose of analyzing a prototype sedentary, semiskilled set of activities. Oxygen consumed above resting metabolic requirement for each of the procedures was (1) sawing, two to two and one-half times, (2) filing and sanding, one and one-half to two times, and (3) assembling, one and two-tenths to two times. Here again no significant differences between the cardiac subjects and the control group were noted. In this series of studies the problems of motivation and purposeful activity have been obviated in large measure, since the end product was a useful and desirable object which the patient took home for use. Sex differences in energy cost were noted since in the female subject the energy cost was at a slightly higher level than in the male subjects. Apparently these were related to the unfamiliarity of the female subject with tools. The data derived indicate that the energy expenditure for a typical sedentary, semiskilled activity is not significantly demanding and that the patient who is classified as I–III can perform them without difficulty.

In the cardiac kitchen energy cost studies have been performed with standardized floor mopping and water-pail lifting and carrying in groups of compensated cardiac women, with noncardiac women of the same age serving as controls. These activities did not require specific skills or training, since they were routinely performed in any kitchen and, indeed, had formed an important pattern in the daily existence of all the subjects studied. The results indicate that the compensated cardiac woman is no less efficient in performance of these activities than the noncardiac. In addition, variations in the methods of performing the same work have revealed technics of energy conservation. The data[26] appear to indicate that kitchen activities for the average cardiac housewife should be limited to those requiring a lower energy cost level than approximately 15 ml. of oxygen per kilogram of body weight (roughly five times the resting rate) for short periods of activity, since most of the cardiac patients developed signs or symptoms during the performance of activities with an energy cost above this level. Extension of such studies is important since this will provide safe work plans for maximum efficiency of cardiac women working in the kitchen.

In an effort to develop a simple objective method of screening which might serve as a possible aid in the determination of functional capacity for rehabilitation of the cardiac subject, it has been recently demonstrated that there is a high degree of positive correlation between the normality of the resting ballisto-

cardiogram (Dock type) and ability to do work of known moderate to marked energy cost (up to 24 times above the resting level) in a group of 51 cardiac patients.[27] Application of the chi-square test to a two-way grouping of the results (excluding borderline and indeterminate cases) showed that the difference in ability to expend energy at known levels between patients with normal and abnormal resting ballistocardiograms was highly significant (p value of less than .001). It is to be understood that no claim is made for quantitation since qualitative observations only were made of the normality or abnormality of the ballistic pattern, using the accepted criteria as outlined in the literature.

The value of the ballistocardiographic method, however, may be limited to those cardiacs who are less than 50 years of age, since it is well known that the ballistocardiogram becomes abnormal with increasing age. This is in accord with the conclusions of others.[28, 29] These age changes are not clearly understood, but the general consensus is that factors other than cardiac may play a role in their production.

Findings such as these may allow for more acurate classification and vocational placement of cardiac patients, since the studies show that under the conditions observed, a normal resting ballistocardiogram in the cardiac patient is very frequently associated with the capacity for moderate to marked energy expenditure. On the other hand, an abnormal resting ballistocardiogram gives no consistent information in this regard. This suggests that the resting ballistocardiogram, when normal, may be (a) a useful tool in evaluating the functional or working capacity of certain groups of cardiac patients for rehabilitation purposes and vocational guidance, and may serve as (b) a screening device for finding those cardiacs, other factors such as psychologic, motivation, and aptitude, being considered, who possess the functional capacity to perform jobs or activities whose energy requirements are known or can be estimated from physical-demands analyses. However, in view of the increasing incidence of abnormality of the resting ballistocardiogram in older age groups, for practical purposes its usefulness may be limited to that segment of the cardiac population under the age of 50 years—a not too inconsiderable group—who are, by virtue of being younger, more suitable for rehabilitation.

Using the methods outlined above and making an attempt to match the capacities of the patient with carefully reviewed physical demands of given selected jobs after aptitude, interest, motivation, and psychologic factors were analyzed, placements have been made of cardiac patients through the J.O.B. Committee—the job finding organization in this Department. Patients with what might be called "intractable iatrogenicity" have not been considered good candidates. It is of interest to note that greatest success has been with smaller industrial organizations where there were no organized medical departments. Rejection of the cardiac patient by larger industries appeared to be on factors other than those endogenous to the patient. Here, questions of seniority, other union practices, workmen's compensation, and other insurance implications seemed to mitigate against acceptance of the worker with cardiac disease for employment. The work experience of those cardiac patients who were selectively placed, usually in jobs which were related in some degree to past vocational experience, has been good to date. Follow-up studies are in progress.

Thinking relative to employment of the cardiac patient must be on a practical and realistic basis, since experience has shown that this problem is minimized in a situation where the labor supply is in short supply, while the converse holds true where the labor supply is adequate. As yet there is no mandatory legislation in this country as exists in England where industry is required by law to hire a certain percentage of disabled personnel. It is to be hoped this will never be necessary. In general, it might be said that American industry has had good experience with the employee whose cardiac disease has been discovered after some years of employment during a company medical survey. Selective placement within the company in a type of work more suited to the cardiac status has often been effected. It is the new employee with heart disease who applies for a job who has experienced the greatest dif-

ficulty in being accepted by industry, especially during times of full labor supply.

Current clinical experience indicates that the assignment of a specific functional classification is often conditioned by the physician's own fears and prejudices about the patient's ability to do work, to say nothing of the latter's anxieties and exaggeration of symptoms. The frequency with which disabling cardiac neurosis (superimposed on nondisabling organic disease) is met with in the cardiac clinic is proof enough of this and is one of the greatest obstacles to the rehabilitation of the cardiac patient. It is hoped that explorations such as those indicated above, as well as the extension of the Work Classification Unit concept into more cardiac clinics, will eventually afford objective information which may aid in refining the functional classification of cardiac patients for more intelligent rehabilitation purposes.[30]

Acknowledgments

We are indebted to the following for access to clinical material: Lewis H. Bronstein, M.D., Chief, Cardiac Clinic, Beekman-Downtown Hospital, and Associate Chief, Work Classification Unit, Adult Cardiac Clinic, Third Medical Division, Bellevue Hospital; Arthur C. DeGraff, M.D., Chief, College Cardiac Clinic, New York University College of Medicine, University Hospital; E. Hugh Luckey, M.D., Director, Second (Cornell) Medical Division, Bellevue Hospital; Charles A. Poindexter, M.D., Chief, Fourth Medical (New York University Postgraduate) Division Cardiac Clinic, Bellevue Hospital; Ada C. Reid, M.D., Director, Cardiac Clinic, New York Infirmary; Charles F. Wilkinson, Jr., M.D., Director, Fourth (New York University Postgraduate) Medical Division, Bellevue Hospital.

The assistance of Henry Brown, M.D., Edith L. Kristeller, M.D., Vilma Smith France, B.A., and Julia Judson, B.S. (Home Economics), M.A., in some of the original studies is gratefully acknowledged.

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AMERICAN SOCIETY FOR THE STUDY OF ARTERIOSCLEROSIS

PROGRAM OF THE SEVENTH ANNUAL MEETING TO BE HELD AT THE KNICKERBOCKER HOTEL IN CHICAGO, ILL., NOVEMBER 1–2, 1953

(All papers except the Principal Address will be limited to 15 minutes for presentation and 5 minutes will be allowed for discussion)

NOVEMBER 1, 1953

Morning

Nelson W. Barker, Presiding

8:15
Registration

9:00
1. A Serologic Method for the Detection and Study of Abnormal Concentrations of Serum Lipoproteins Associated with Atherosclerosis. S. P. Baker and E. Ogden, Department of Physiology, College of Medicine, The Ohio State University, Columbus, Ohio.

9:20
2. Squalene Feeding in Experimental Atherosclerosis. D. Kritchevsky, A. W. Moyer, W. C. Tesar, J. B. Logan, R. A. Brown, and G. Richmond, Viral and Rickettsial Research, Lederle Laboratories Division, American Cyanamid Company, Pearl River, N. Y.

9:40
3. The Origin of Aortic Phospholipid in Rabbit Atheromatosis. D. B. Zilversmit, M. L. Shore, and R. F. Ackerman, Divisions of Physiology, Preventive Medicine and Medicine, University of Tennessee, Memphis, Tenn.

10:00
4. Principal Invited Address: Arteriosclerosis and Epidemiology. J. Watt, Director, National Heart Institute, National Institutes of Health, U. S. Public Health Service, Bethesda, Md.

11:00
5. Fecal Bile Acids of Cholesterol-Fed Dogs. E. H. Mosbach, L. Abell, and F. E. Kendall, Research Service, First (Columbia University) Division, Goldwater Memorial Hospital, and the Department of Biochemistry and Medicine, College of Physicians and Surgeons, Columbia University, New York, N. Y.

11:20
6. Serum Lipoproteins in the Pathogenesis of Experimental Atherosclerosis. J. H. Bragdon and E. Boyle, National Heart Institute, Bethesda, Md.

11:40
7. Metabolism of Cholesterol-4-C^{14} in Hypercholesterolemia. L. Hellman, R. Rosenfeld, T. F. Gallagher, D. Adlersberg and Chun-I Wang, Sloan-Kettering Institute for Cancer Research, and Mount Sinai Hospital, New York, N. Y.

NOVEMBER 1, 1953

Afternoon

Russell L. Holman, Presiding

2:00
Business Session

2:20
8. Presidential Address. Dr. Nelson W. Barker.

2:40
9. The in Vitro Production of Lipemia Clearing Factor. R. K. Brown and D. L. Kauffman, Laboratory of Cellular Physiology, National Heart Institute, Bethesda, Md.

3:00
10. Purification of Clearing Factor by Substrate-Complex Formation. C. B. Anfinsen, Jr., and T. W. Quigley, Jr., Laboratory of Cellular Physiology, National Heart Institute, Bethesda, Md.

3:20
11. Sex Difference in Cholesterol-Induced Coronary Atherogenesis in Mature Chickens: Its Determination by Endogenous Estrogen Secretion. R. Pick, J. Stamler, and L. N. Katz, Cardiovascular Department, Medical Research Institute, Michael Reese Hospital, Chicago, Ill.

3:40
12. Further Studies on Estrogen Prophylaxis of Cholesterol-Induced Coronary Atherogenesis. J. Stamler, R. Pick, and L. N. Katz, Cardiovascular Department, Medical Research Institute, Michael Reese Hospital, Chicago, Ill.

4:00
13. Localization of Lipids in Injured Coronary Arteries of Dogs Following Injection of Egg-Yolk Fractions or of Hyperlipemic Human Plasma. L. L. Waters, Department of Pathology, Yale University School of Medicine, New Haven, Conn.

4:20
14. Allylamine Induced Coronary Artery and Aortic Lesions in Dogs Demonstrated by Polysaccharide Staining. L. L. Conrad, W. Joel, and R. H. Furman, Oklahoma Medical Research Institute and Hospital, and the Department of Pathology, Oklahoma University School of Medicine, Oklahoma City, Okla.

4:40
15. Atherosclerosis: Further Experiences in the Perfusion of Normal Blood Vessels with Human Blood. S. M. Evans, H. K. Ihrig, W. Zeit, K. D. Brown, D. Mountain, N. Hazelwood, and E. R. Haushalter, Department of Anatomy, Marquette University School of Medicine, Milwaukee, Wis.

5:00
16. Ultraviolet Irradiation and Cholesterol Metabolism. R. Altschul and I. H. Herman, University of Saskatchewan and St. Paul's Hospital, Saskatoon, Sask., Canada.

6:30
Cocktails.

7:30
Annual Dinner.

NOVEMBER 2, 1953

Morning

Louis N. Katz, Presiding

8:30
Registration

9:00
17. Prevalence of Arteriosclerosis in A Working Population. F. H. Epstein and E. P. Boas, Research Department, Sidney Hillman Health Center, New York, N. Y.

9:20
18. The Association between the Habitual Diet and the Incidence of De-

GENERATIVE HEART DISEASE IN DIFFERENT POPULATIONS. A. Keys, Laboratory of Physiological Hygiene, University of Minnesota, Minneapolis, Minn.

9:40

19. OBESITY AND SERUM LIPIDS. J. Pomeranze, R. J. Lucarello, and A. A. Goldbloom, New York Medical College and the Flower and Fifth Avenue Hospitals, and Metropolitan Hospital, New York, N. Y.

10:00

20. LIPOPROTEIN STUDIES IN DIABETICS WITH ARTERIOSCLEROTIC DISEASE. W. S. Collens, M. M. Banowitch, and J. Colsky, Medical Services Maimonides Hospital, Brooklyn, N. Y.

10:20

21. THE DIABETIC TRIOPATHY. H. F. Root, Joslin Clinic, Boston, Mass.

10:40

22. BIOLOGIC VARIABILITY OF HUMAN SERUM BETA LIPOPROTEINS AND TOTAL CHOLESTEROL IN LATE MATURITY AND OLD AGE. D. M. Watkin, E. Y. Lawry, and G. V. Mann, Section on Gerontology, National Heart Institute, Bethesda; Baltimore City Hospitals, Baltimore, Md; and the Department of Nutrition, Harvard University School of Public Health, Boston, Mass.

11:00

23. THE SERUM LIPIDS AND SERUM URIC ACID IN NORMAL MEN AND WOMEN PAST THE AGE OF 65 YEARS. M. M. Gertler and B. S. Oppenheimer, Home for Aged and Infirm Hebrews of New York City, New York, N. Y.

11:20

24. ANALYSIS OF JUVENILE ATHEROSCLEROSIS. R. L. Holman and J. P. Strong, Department of Pathology, Louisiana State University School of Medicine, The Charity Hospital of Louisiana, and the Coroner's Office of Orleans Parish, New Orleans, La.

11:40

25. CHOLESTEROL AND VASCULAR RESPONSES TO INDUCTION OF "COARCTATION" OF AORTA IN CHICKS. S. Rodbard and C. Bolene-Williams, Cardiovascular Department, Medical Research Institute, Michael Reese Hospital, Chicago, Ill.

12:00

26. A COMPARISON OF MORPHOLOGICAL AND CHEMICAL METHODS OF GRADING CORONARY ARTERIOSCLEROSIS. J. C. Paterson and B. R. Cornish, Department of Medical Research, the Collip Medical Research Laboratory, the University of Western Ontario, London, Ontario, Canada.

NOVEMBER 2, 1953

Afternoon

James C. Paterson, Presiding

2:00

27. LIPOPROTEIN STUDIES ON HUMANS SUBJECTED TO CONTROLLED DIETARY REGIMENS WITH SUBTRACTION AND ADDITION OF FATS, SITOSTEROL AND DIHYDROCHOLESTEROL. E. Boyle, C. F. Wilkinson, Jr., R. S. Jackson, and M. R. Benjamin, Laboratory of Metabolism, National Heart Institute, Bethesda, Md.; the Department of Medicine, New York University Post-Graduate Medical School; and the Fourth Medical (NYU) Division, Bellevue Hospital, New York, N. Y.

2:20

28. THE EFFECT OF VARYING THE INTAKE OF DIETARY FAT AND THE INGESTION OF SITOSTEROL ON THE LIPID FRACTIONS OF HUMAN SERUM. C. F. Wilkinson, E. Boyle, R. S. Jackson, and M. R. Benjamin, Department of Medicine, New York University Post-Graduate Medical School, New York; the Fourth Medical (NYU) Division, Bellevue Hospital, New York, N. Y.; and the Laboratory of Metabolism, National Heart Institute, Bethesda, Md.

2:40

29. EFFECTS OF HEPARIN ON PLASMA LIPIDS IN NORMAL PERSONS, AND IN PATIENTS WITH CORONARY ATHEROSCLEROSIS, NEPHROSIS AND PRIMARY HYPERLIPEMIA. J. Herzstein,

Chun-I Wang, and D. Adlersberg, Mount Sinai Hospital, New York, N. Y.

3:00

30. Hypocholesterolemic Effect of a Brain Fraction in Patients with Elevated Serum Cholesterol. R. J. Jones, Department of Medicine, University of Chicago, Chicago, Ill.

3:20

31. The Effects of Smoking and of Nicotine on the Ballistocardiograms of Normal Subjects and Patients with Coronary Artery Disease. F. W. Davis, Jr., W. R. Scarborough, R. E. Mason, M. L. Singewald, and B. M. Baker, Jr., Physiological Division, Department of Medicine, the Johns Hopkins Hospital, Baltimore, Md.

3:40

32. The Diagnostic Value of Serum Cholesterol Determination, Ultracentrifuge Studies and Chylomicron Levels in Fasting Serum. T. D. Labecki, Heart Disease Control Unit, Mississippi State Board of Health, Jackson, Miss.

4:00

33. Coronary Artery Lesions in Sudden Death. S. H. Durlacher, A. J. Fisk, R. S. Fisher, and W. V. Lovitt, Jr., Department of Pathology, Louisiana State University School of Medicine, New Orleans, La.; and the Department of Legal Medicine, University of Maryland School of Medicine, Baltimore, Md.

4:20

34. Effects of Cholesterol on Anti-lipfanogen and Lipfanogen Levels in Vitro. H. S. Simms, C. R. Harmison, and R. B. Best, College of Physicians and Surgeons, Columbia University, New York, N. Y.

4:40

35. Serum Lipid and Protein Fractions. IX. Comparisons of Ninety-Six Patients with Vascular Disease and Sixty Normal Controls (with Additional Notes on Blood Donors). I. Leinwand and D. H. Moore, New York University–Bellevue Medical Center, St. Clare's Hospital and College of Physicians and Surgeons, Columbia University, New York, N. Y.

Demonstration

Chromatographic Partition of Serum Proteins, Protein-Bound Lipids and Protein-Bound Carbohydrates in Rabbits, before, during and after Cholesterol Feeding. O. J. Pollak and G. Chubaty, Kent General Hospital, Dover, Del.

TO BE READ BY TITLE

36. Further Studies of Human Circulating Plasma Heparin Levels.—Correlation with Serum Lipids and Lipoproteins. H. Engelberg, Division of Laboratories, Cedars of Lebanon Hospital, Los Angeles, Calif.

37. Pentapyrrolidinium (M & B 2050) in the Treatment of Severe Hypertension. E. D. Freis, E. A. Partenope, and J. C. Rose, Georgetown University and Veterans Administration Hospitals, Washington, D. C.

38. Some Observations on the "Clearing" of Artificial Emulsions Induced by Pre- and Post-Heparin Serum from Normal and Diabetic-Atherosclerotic Subjects. R. H. Furman and L. L. Conrad, Oklahoma Medical Research Institute and Hospital, Oklahoma City, Okla.

39. Revascularization of the Myocardium by Cardiopexy in the Treatment of Coronary Artery Disease. A. N. Gorelik and S. Dack, New York, N. Y.

40. Fat Loading Studies in Relation to Age. J. Herzstein, Chun-I Wang, and D. Adlersberg, Mount Sinai Hospital, New York, N. Y.

41. Hyperbeta-globulinemia Connected with Hypoalbuminemia in Arteriosclerosis and Coronary Sclerosis. T. Kheim, P. G. Ackermann, and W. B. Kountz, Division of Gerontology, Washington University School of Medicine, and the St.

Louis City Infirmary Hospital, St. Louis, Mo.

42. Effects of Specific Steroids and Phosphatides upon the Levels of Plasma Lipids. L. W. Kinsell, G. C. Cochrane, H. E. Balch, and N. Foreman, Institute for Metabolic Research of the Highland Alemeda County Hospital, Oakland, Calif.

43. Diffusion Coefficients of Some Gases and Non-Gaseous Solutes in Human Arterial Tissue. J. E. Kirk, S. P. Chiang, and T. S. Laursen, Division of Gerontology, Washington University School of Medicine, St. Louis, Mo.

44. Serum Lipid and Protein Fractions. VII. Lipid Transport in the Human as Determined by Electrophoresis of the Proteins. I. Leinwand, New York University–Bellevue Medical Center, St. Clare's Hospital and College of Physicians and Surgeons, Columbia University, New York, N. Y.

45. Serum Lipid and Protein Fractions. VIII. The Variability of the Pattern of the Lipid Protein Relationship. I. Leinwand and D. H. Moore, New York University–Bellevue Medical Center, St. Clare's Hospital and College of Physicians and Surgeons, Columbia University, New York, N. Y.

46. Serum Lipid and Protein Fractions. X. The Electrophoretic Pattern and Lipid Relationship in some Experimental Animals and Man. I. Leinwand and D. H. Moore, New York University–Bellevue Medical Center, St. Clare's Hospital and College of Physicians and Surgeons, Columbia University, New York, N. Y.

47. Effects of Ovariectomy on Experimental Atherosclerosis in Rabbits. G. Mininni, S. Contro and C. Checchia, Department of Internal Medicine, University of Florence Medical School, Florence, Italy.

48. Interrelationships Between Plasma Lipids and Atherosclerosis in Residents of a Home for the Aged. A. Pick, S. Rosenblum, and L. N. Katz, Cardiovascular Department, Medical Research Institute, Michael Reese Hospital, and Drexel Home (formerly Home for Aged Jews), Chicago, Ill.

49. Enteric Factors in Cholesteremia and Atherosclerosis. S. Rodbard and L. N. Katz, Cardiovascular Department, Medical Research Institute, Michael Reese Hospital, Chicago, Ill.

50. Observations on the Stability of Serum Lipids. P. B. Roen, E. W. Townsend, and J. W. Perry, Clinic for the Study of Arteriosclerosis, Hollywood Presbyterian Hospital, Los Angeles, Calif.

51. The Surgical Treatment of Neurotrophic Plantar Ulcers in Arteriosclerotics. B. C. Smith, New York, N. Y.

52. Importance of the Effects of Heparin and Antiheparins on Lipemia. J. J. Spitzer, B. D. Bond, and E. R. Grunwald, Department of Physiology, Florida State University, Tallahassee, Fla.

53. Effects of ACTH on Plasma Lipids and Atherogenesis in Cholesterol-Fed Chicks. J. Stamler, R. Pick, and L. N. Katz, Cardiovascular Department, Medical Research Institute, Michael Reese Hospital, Chicago, Ill.

54. Failure of Vitamin E, Vitamin B_{12} and Pancreatic Extracts to Influence Plasma Lipids and Atherogenesis in Cholesterol-Fed Chicks. J. Stamler, R. Pick, and L. N. Katz, Cardiovascular Department, Medical Research Institute, Michael Reese Hospital, Chicago, Ill.

55. Atherosclerotic Stenosis of the Lower Abdominal Aorta. J. B. Wolffe, Department of Medicine, Valley Forge Heart Institute and Hospital, Fairview Village, Pennsylvania; and Wolffe Clinic, Philadelphia, Pa.

PROCEEDINGS OF THE SEVENTH ANNUAL MEETING OF THE AMERICAN SOCIETY FOR THE STUDY OF ARTERIOSCLEROSIS

ABSTRACTS

1. A Serologic Method for the Detection and Study of Abnormal Concentrations of Serum Lipoproteins Associated with Atherosclerosis

Saul P. Baker and Eric Ogden

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Thiouracil-cholesterol atherogenic diets have produced abnormal serum lipoproteins and lipoprotein concentrations in dogs. Serum fractions containing these lipoproteins have been used to develop a simple serologic test for detecting abnormal serum lipoprotein concentrations in dogs. By immunizing rabbits with a fraction containing S_f 2–30 lipoproteins ultracentrifugally obtained from the serum of a dog on a thiouracil-cholesterol atherogenic diet, immune sera have been produced which will detect the abnormally increased concentrations of these serum lipoproteins in these dogs.

Effects of atherogenic diet and thyroidectomy on the S_f 2–30 serum lipoproteins of dogs have been studied utilizing the precipitin technic. Abnormal concentrations of S_f 2–30 serum lipoproteins have been detected after only one week on diet, and have persisted as long as 10 weeks after the dogs have been returned to a stock control diet. These results have been compared with serum cholesterol concentrations and autopsy findings.

Sera of normal dogs on stock diets and of the experimental dogs during the initial control period on stock diet consistently demonstrated a lipoprotein concentration significantly less than that observed in the case of the dogs while on the experimental regimens.

Sera from three men in whom no vascular disease had been detected did not react with the immune rabbit sera; but sera from one man with proven atherosclerosis did react in high titer with the immune rabbit sera.

2. Squalene Feeding in Experimental Atherosclerosis

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The hydrocarbon squalene has been suggested as the obligatory precursor of cholesterol. Other workers have shown that in animals fed squalene there is a large increase in liver nonsaponifiable components and in liver cholesterol. The purpose of this experiment was to test whether this compound is as efficient in producing atherosclerosis in rabbits as is cholesterol. If it is as efficient, and inasmuch as cholesterol produced from fed squalene may be regarded as endogenous, then it would indicate that excess production of endogenous cholesterol is sufficient to cause atheromatosis. If squalene does not produce atherosclerosis as rapidly or severely as does cholesterol, then exogenous cholesterol would be indicated as the more important causative agent in atheromatosis. The results might indicate some relationship between exogenous and endogenous cholesterol in this respect.

Four groups of rabbits were used. The first group received a normal diet. In the other three groups the normal diet was augmented with 3 per cent squalene in corn oil, 3 per cent cholesterol in corn oil and 3 per cent squalene plus cholesterol in corn oil, respectively. The squalene alone did not cause atherosclerosis, but fed with cholesterol did not prevent it.

The severity of atherosclerotic lesions, serum lipoprotein levels and liver nonsaponifiable components for all groups were determined and will be presented and discussed.

3. The Origin of Aortic Phospholipid in Rabbit Atheromatosis

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Normal rabbits and rabbits maintained on a high cholesterol diet for five months were injected with P^{32}. Six hours later the concentration and radioactivity of phospholipids in liver, plasma and aorta were measured. The rate of phospholipid synthesis in liver of the cholesterol-fed animals was not markedly altered whereas the rate of exchange of phospholipid between liver and plasma was accelerated in these experimental animals. The amount of phospholipid in the atherosclerotic aorta was four and one-half times as large as in the control aorta. The amount of phosphate incorporated in the aorta phospholipid was six to seven times greater in the cholesterol-fed rabbits. Since the specific activity of aortic phospholipid was much higher than the average or final specific activity of the plasma phospholipids in the cholesterol-fed animals, it appears that the arterial phospholipids were not derived from plasma. These preliminary data indicate that atherogenesis in rabbits is accompanied by a marked stimulation of phospholipid synthesis in the aorta and it appears that the phospholipids of the plaque which constitute about 15 per cent of its total lipids are synthesized in the arterial wall.

4. Arteriosclerosis and Epidemiology

J. Watt

Director, National Heart Institute, National Institutes of Health, United States Public Health Service, Bethesda, Md.

5. Fecal Bile Acids of Cholesterol-Fed Dogs

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The fate of dietary cholesterol in dogs is under investigation. It has been found that dogs fed 10 Gm. of cholesterol a day, either with or without thiouracil, excrete in their feces between 2 and 5 Gm. of nonsaponifiable lipids consisting largely of sterols. This rate of excretion is maintained even though the animal is continued on the regimen for years. The difference between cholesterol intake and excretion cannot be due to storage in tissues. In prolonged experiments the amount unaccounted for exceeds the dry weight of the animal. Methods have been developed for the isolation and identification of fecal bile acids. Dogs excrete between 120 and 170 mg. of bile acid per day on a normal diet and between 100 and 260 mg. on the cholesterol-thiouracil regimen. These results show that a major portion of the ingested cholesterol is not ex-

creted as bile acids, but they do not eliminate the possibility that bile acids may be intermediates in the metabolic degradation of dietary cholesterol. A change in the ratio of cholic acid to desoxycholic acid from 9:1 in fistula bile to 1:3 in the feces shows that the bile acids are not inert in the alimentary tract.

6. Serum Lipoproteins in the Pathogenesis of Experimental Atherosclerosis

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The low-density lipoproteins from the serum of cholesterol-fed rabbits were isolated in the preparative ultracentrifuge and injected intravenously in rats. Focal deposits of sudanophilic material appeared within the arterial intima within a few hours. When the lipoproteins were injected daily over a period of weeks, large focal accumulations of foam cells appeared. Most of these regressed completely in time, but some remained as areas of fibrous thickening containing anisotropic crystals. Repeated daily injections of synthetic cholesterol emulsions or of triglyceride emulsions produced no lesions. Injection of egg yolk, in doses of lipid equivalent to those of serum lipoproteins, produced deposits without cellular proliferation.

Normal and "abnormal" lipoproteins from human sera were also isolated in the ultracentrifuge and injected intravenously in rats. The rats were examined five hours later. Chylomicrons and the highest S_f classes disappear very rapidly from the circulation and no sudanophilic deposits are found within the vessels. When S_f 10–100 classes are injected, they are removed more slowly from the circulation and focal deposits of sudanophilic material are found within the vessel walls. When S_f 2–8 and alpha lipoproteins are injected, they are removed extremely slowly. Evidence to date indicates that these classes do not produce lesions. The situation is complicated, however, by the fact that large doses of these classes are followed by the appearance of S_f 10–100 lipoproteins in the recipient's serum.

7. Metabolism of Cholesterol-4-C^{14} in Hypercholesterolemia

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In an attempt to differentiate between the behavior of plasma cholesterol in patients with hypercholesteremia and in subjects with normal cholesterol levels, cholesterol-4-C^{14} was fed to three patients with idiopathic familial hypercholesteremia and to two patients with normal cholesterol levels. Plasma free and ester cholesterol were separately isolated and their specific activities were measured over a period of three months.

The maximum specific activity of free cholesterol was reached in eight-tenths to two days when from 15 to 25 per cent of the administered cholesterol was in the circulating plasma. The ester cholesterol had an initially lower level of radioactivity and reached its peak specific activity at two to three days, which was equal at that point to the specific activity of the free cholesterol. Beyond this intersection, the specific activities of free and ester cholesterol declined at about the same rate. The specific activity of the ester cholesterol continued to exceed that of the free cholesterol throughout the period of observation. The fact that the specific activities of the free and ester cholesterol were never identical after the intersection at the peak value of the ester suggests that the pool of ester cholesterol is physiologically distinct from that of free cholesterol. From mathematical considerations, the curves for the decline in radioactivity of the free and ester cholesterols suggests that the free cholesterol is the direct precursor of the esterified form.

Of the radioactivity administered as cho-

lesterol 25 to 60 per cent was recovered in the feces over a 14 day period and 0.5 to 2.5 per cent appeared in the urine.

This method of study fails to disclose any significant difference in the turnover of plasma cholesterol in patients with idiopathic hypercholesteremia as compared with the control subjects.

8. Presidential Address

Nelson W. Barker

9. The in Vitro Production of Lipemia Clearing Factor

Ray K. Brown and Dorothy L. Kauffman

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Lipemia clearing factor may be formed in vitro from a precursor found in plasma, a tissue factor found in rat or mouse pylorus, and heparin or heparinoids. The chemical and enzymatic properties of in vitro produced clearing factor are identical with the properties of clearing factor produced by heparin injection into animals.

Tissue factor is prepared by carbon dioxide freezing, grinding and freeze drying rat or mouse pylorus. Ball milling the dry powder and extraction with 60 per cent glycerol in water yield a residue of higher purity. Inactive preparations may be activated by incubation with cysteine or British anti-lewisite. Mercuric chloride and parachloromercuribenzoate 10^{-4}M inhibit clearing factor formation. These findings suggest that tissue factor is a sulfhydryl enzyme. With some preparations of tissue factor a lag of one half to two hours occurs before clearing activity is evident. The length of the lag period is inversely related to the tissue factor concentration.

Precursor has the ultracentrifugal properties of an alpha lipoprotein although only a relatively small proportion of the alpha lipoproteins disappear during the clearing factor forming reaction. The amount of clearing factor formed is proportional to the precursor concentration, at low concentrations. Further studies on the chemical changes occurring during clearing factor production and on the properties of tissue factor and precursor will be reported.

10. Purification of Clearing Factor by Substrate-Complex Formation

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Kinetic studies on the decrease in turbidity of coconut oil emulsions under the action of partially purified components of the lipemia clearing system have suggested that complex formation occurs between the substrate particles and clearing factor. This possibility was strengthened by the observation that clearing factor activity appeared to complex nonspecifically with both high and low density lipoproteins when studied ultracentrifugally. The complexing phenomenon has now been made the basis for an efficient and simple purification procedure. Equal volumes of a Tween-60 stabilized 1 per cent coconut oil emulsion (Abbott Laboratories) and clearing factor containing plasma are incubated in the cold for 30 minutes. The mixture is then layered under 0.5 volumes of water in plastic Spinco-Model L No. 30 tubes and centrifuged at 30,000 revolutions per minute for one half hour. The oil layer is harvested using the "tube-slicer" technic and, after dilution to approximately half the original plasma volume with water, is mixed with dry nonsoluble potato starch (Amend. 100 mg. per cubic centimeter plasma) and thoroughly lyophilized. The resulting completely dry powder is extracted at −20 C. with three changes of hexane. After removal of the last traces of hexane in vacuo, this powder is suspended in

dilute phosphate buffer or ammonia solution (pH 7–9) at 0 C. for 15 to 30 minutes. The colorless supernatant obtained contains approximately half the original clearing factor activity at a purification level of 100 to 200 fold. Studies on the heparin content and enzymatic behavior of this preparation will be presented.

11. Sex Difference in Cholesterol-Induced Coronary Atherogenesis in Mature Chickens: Its Determination by Endogenous Estrogen Secretion

R. Pick, J. Stamler, and L. N. Katz

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Since exogenous estrogens prevent cholesterol-induced coronary atherogenesis in cockerels, an experiment was undertaken to assess the influence of the endogenous estrogen secretion of egg-producing hens, and to compare atherogenesis in mature male and female chickens.

Four groups of 28 week old birds were studied: (1) intact egg-laying females; (2) oviduct-ligated females, exhibiting intraperitoneal deposition of egg yolks; (3) intact males; (4) castrate males. Oviduct ligation was accomplished to intensify hypercholesterolemia by preventing disposal of cholesterol via egg-laying. The following responses to cholesterol feeding were observed: group 1, a moderate hypercholesterolemia with normal total cholesterol/lipid phosphorus (C/P) ratio; group 2, more marked hypercholesterolemia with normal C/P ratio; group 3, hypercholesterolemia similar in degree to group 2, with elevated C/P ratio; group 4, most marked hypercholesterolemia with elevated C/P ratio. Groups 1 and 2 exhibited prophylactic inhibition of coronary atherogenesis, in contrast to groups 3 and 4.

It is concluded that endogenous estrogen secretion at the physiologic level in egg-producing hens is capable of protecting the coronary vessels against cholesterol-induced atherogenesis.

12. Further Studies on Estrogen Prophylaxis of Cholesterol-Induced Coronary Atherogenesis

J. Stamler, R. Pick, and L. N. Katz

From the Cardiovascular Department, Medical Research Institute, Michael Reese Hospital, Chicago, Ill.

Previous work from this department demonstrated that both parenteral estradiol and oral mixed conjugated estrogens (Premarin) effectively prevent cholesterol-induced coronary atherogenesis in cockerels. This report summarizes some recent experiments designed to investigate the parameters and mechanisms of this phenomenon.

In one study, cockerels were pretreated with estradiol for three weeks prior to exhibition of a cholesterol-supplemented diet. Hormone administration was discontinued with onset of cholesterol feeding. The resultant plasma hyperlipemia was typically of the cholesterol-induced type, with no evidence of an estrogen effect. Nevertheless, partial inhibition of coronary atherogenesis apparently occurred.

Parenteral diethylstilbestrol had the same triad of effects on secondary sex characteristics, plasma lipids and coronary atherogenesis as estradiol or Premarin. In contrast, several other structurally related synthetic compounds of low estrogenic potency had no influence on lipids or atherogenesis.

With the simultaneous administration of Premarin and an adrenal steroid (desoxycorticosterone acetate, cortisone, hydrocortisone) or corticotropin, the triad of estrogen effects was preserved.

Cholesterol-fed rabbits given Premarin in the drinking water apparently exhibited no inhibition of coronary atherogenesis, in association with no significant effects on plasma lipid patterns or aorta atherogenesis.

13. Localization of Lipids in Injured Coronary Arteries of Dogs Following Injections of Egg-Yolk Fractions or of Hyperlipemic Human Plasma

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Experimental foam-cellular lesions of the coronary arteries of dogs, that follow the intravenous injections of allylamine together with egg-yolk emulsions have been described previously. The present report deals with an extension of these investigations. A principal phospholipoprotein of egg yolk, ovovitellin, has been prepared. This substance can be injected intravenously into dogs as a suspension in physiologic saline. It has a very low cholesterol content, in contrast to whole egg yolk. Injection of this material repeatedly into normal dogs, or into dogs with coronary arteries previously injured by allylamine, was followed by a progressive rise of the plasma cholesterol and of other lipid fractions of the blood. Foam-cellular fatty lesions of the injured coronary arteries occurred as with the injection of whole egg yolk, but at much lower blood lipid levels. These lesions gave positive Schultz reactions for cholesterol.

Because of the occurrence in the experiments above of fatty, foam-cellular lesions in the injured coronary vessels at relatively low blood cholesterol levels, hyperlipemic plasma (alimentary lipemia) from normal humans was injected repeatedly into dogs with injured coronary arteries. Difficulty was encountered, because of dilution factors and because of rapid removal, in even nearly approaching in the dogs' blood the levels of lipemia present in the donor plasmas. Nevertheless an increase in plasma cholesterol greater than can be obtained acutely by feeding resulted. Large quantities of lipid were localized in areas of injury of the coronary arteries giving rise to fatty lesions similar to those following injections of egg yolk or egg-yolk fractions.

14. Allylamine Induced Coronary Artery and Aortic Lesions in Dogs Demonstrated by Polysaccharide Staining

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Observations have been made on 19 dogs given hydrochloric acid-neutralized allylamine in doses of 15 to 25 mg. per kilogram for 1 to 25 days (three times weekly).

Aortic lesions consisted of marked acid polysaccharide staining (Hale) of the "ground substance" in the inner third of the media, especially just beneath the intima, with some fluid accumulation tending to separate elastic fibers. Occasionally the only change noted in coronary arteries (usually large epicardial branches) was an increase in acid polysaccharide staining material. In contrast to the aorta, this material did not tend to concentrate in the inner media. The impression is gained that acid polysaccharide material is more peripherally distributed in right as opposed to left coronary arteries. Coronary arteries (small penetrating branches, especially in papillary muscles of left ventricle) may show eosinophilic change in the media (fibrinoid necrosis) resembling periarteritis nodosa. Other areas show medial thickening with increased cellularity and lymphocytic and monocytic perivascular accumulation resembling Aschoff cells. No intimal proliferation or separation was noted. Occasionally, swelling of intimal endothelial cells was noted. Foam cells were not seen. Small foci of recent myocardial infarcts, manifested by deep red staining with some loss of muscle nuclei, were noted.

These observations extend our present knowledge of allylamine induced vascular lesions.

15. Atherosclerosis: Further Experiences in the Perfusion of Normal Blood Vessels with Human Blood

S. M. Evans, K. K. Ihrig, W. Zeit, K. D. Brown, D. Mountain, N. Hazelwood, and E. R. Haushalter

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At the 1952 meetings of this society, a technic for pulsating human blood against human postmortem aortas under standardized conditions was described. Preliminary correlations between changes so induced in these vessel walls and the clinical sources of the blood were presented.

Since this report, more than 2,500 single experiments have been conducted with continuing significant correlation. This report deals with these experiences under several different classifications.

1. One hundred eighty-two bloods obtained from donors at the local blood bank are reported by age and sex. Eight per cent of over-all bloods were positive.

2. Six hundred plus atherosclerotic clinical cases are carefully studied by this and other means and the data correlated. The over-all percentage of positivity exceeds 75 per cent.

3. A variety of human membranes and the vessel walls of several animal species are compared with human aortas in an effort to find a suitable substitute. Beef aorta offers the most promise.

4. The effect of variation in the standardized conditions of the experiment is reported.

Conclusion. The method of pulsant perfusion of vessel walls offers promise as a method for evaluation of the atherogenic potential of human blood.

16. Ultraviolet Irradiation and Cholesterol Metabolism

Rudolf Altschul and Irving H. Herman

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Ultraviolet irradiation of cholesterol and, even more so, of dried egg yolk, decreases their atherogenic effect in rabbits (Altschul, 1950). Also irradiation of the rabbits themselves, which are given nonirradiated cholesterol, inhibits the arteriosclerosis which would develop without irradiation (Altschul, 1953). Ultraviolet irradiation reduces almost immediately the blood cholesterol in cancer patients (Malczynski) in contrast to healthy persons where no change or a rise occur (Malczynski; Laurens). Hubert has found that serum cholesterol decreases after ultraviolet irradiation not only in cancer patients, but also in acute infections, pregnancies, and in rare cases of skin pigmentation.

We have determined the serum cholesterol in 30 "arteriosclerotic" persons (coronary thrombosis, hemiplegia, hypertension, diabetes, advanced age) before and after one single ultraviolet irradiation and found in all but one of them two hours after irradiation a decrease of serum cholesterol. The same result was obtained in all but four of them 24 hours after the irradiation. The average maximal reduction was 12.8 per cent (240 mg. per 100 cc. to 209 mg. per 100 cc.) with a standard error of ± 1.7. The normal variation of serum cholesterol is ± 6 per cent (Hubert).

17. Prevalence of Arteriosclersois in a Working Population

Frederick H. Epstein and Ernst P. Boas

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We are studying the prevalence of arteriosclerosis in a random sample of employed men and women aged 40 or over who are members of a union comprising 32,000 garment workers. This preliminary report is based on the findings in 242 men (average age 58) and 105 women

(average age 53). The diagnosis of arteriosclerosis was based on evidence of coronary artery disease, x-ray demonstration of calcification of the thoracic or abdominal aorta, obliterating arteriosclerosis of the extremities and cerebrovascular accident.

Forty per cent of the men and 23 per cent of the women showed one or more of the stated stigmata of arteriosclerosis. Coronary artery disease was found in 18 per cent of the men and 4 per cent of the women, aortic calcification in 27 per cent of the men and 18 per cent of the women, and peripheral vascular disease in 3 per cent of the men and none of the women. In 20 per cent of the men and 18 per cent of the women, aortic calcification was the only evidence of arteriosclerosis. There was no statistically significant difference in the frequency of coronary artery disease between men with aortic calcification and those without calcification.

As regards associated conditions, 24 per cent of the men and 35 per cent of the women had hypertension; for diabetes, the corresponding figures are 5 and 10 per cent. Further data are being collected to permit a breakdown of these figures into age groups and the different ethnic groups studied (predominantly Italian and Jewish). Information concerning serum lipid relationships, diet and genetic factors will also be available for analysis.

18. The Association between the Habitual Diet and the Incidence of Degenerative Heart Disease in Different Populations

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Data on death rates from all causes and rates of death ascribed to cardiovascular disease in men of given ages in various countries have been assembled and analyzed. They show, over the age range of about 30 to 70 years, that the American white male has a higher death rate from all causes than in many other countries and that this is accounted for by an excessive incidence of degenerative heart disease. Data on the national diets show a striking association between total fat consumption and cardiac mortality among men. Studies on serum cholesterol and individual diets in various countries are compatible with the theory of a direct relationship between dietary fat, serum cholesterol and disposition to degenerative heart disease. In two countries (United States and Italy) electrocardiographic studies on men currently clinically healthy show different age trends and this difference is consistent with the theory, developed from other findings, that the relative incidence of degenerative heart disease in a population may be predicted to a considerable extent from characteristics found in samples of clinically healthy men in that population.

19. Obesity and Serum Lipids

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There is a statistically significant relationship between obesity and atherosclerosis, and serum lipid abnormalities and atherosclerosis. However, tissue lipid abnormalities, measured as excessive fat deposits in obesity, and serum cholesterol abnormalities have not been demonstrated as related mechanisms in atherogenesis. Rapid reduction of weight has not demonstrably altered serum cholesterol levels.

To further evaluate the relationship of complete serum lipid partitions, obesity, weight reduction and marked fat restriction, a series

of experiments with human subjects was undertaken:

1. A eucaloric diet containing less than 20 Gm. of fat per day was fed to three groups of three subjects each for periods up to six weeks: (a) three clinically normal subjects with normal serum lipid values; (b) three clinically normal subjects with abnormal serum lipid values; and (c) three subjects with positive clinical evidence of coronary atherosclerosis.

2. A group of 10 moderately obese subjects were fed a 1000 to 1500 calorie reducing diet containing 60 or more Gm. of fat per day for five weeks.

3. A group of 11 obese subjects all of whose initial weight was 250 pounds or more were observed on a 1200 to 1500 calorie diet for periods up to 50 weeks.

Serial serum lipid fractions and fat tolerance tests using 7½ ounces of fat in a breakfast meal were done.

Results: (1) Serum cholesterol levels are unaltered during acute intake of large amounts of fat and cholesterol. (2) Serum lipids fell significantly in all subjects observed on a eucaloric diet containing less than 20 Gm. of fat per day. (3) No significant change in serum lipids was noted in the group of moderately obese subjects observed for a five week period, although significant loss of weight was noted. (4) Serum cholesterol and phospholipid levels were at the lower levels of normal in the grossly obese individuals. However, fatty acid and total lipids appeared significantly higher. A decreased tolerance for the fatty meal was also noted, the curve for serum fatty acids and total lipids reaching much higher levels and being more prolonged than normals. This abnormality tended to correct itself following significant weight loss.

20. Lipoprotein Studies in Diabetics with Arteriosclerotic Disease

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A study of the lipoprotein concentration in the blood of the S_f 12–20 class and 20–100 class as determined by ultracentrifuge was made in 50 diabetics. These were all patients in whom definitive evidence of the existence of arteriosclerotic disease was documented and in whom clinical syndromes arising from degenerative disease affecting either cerebral, renal, or coronary arteries or the arteries of the lower extremities were established. A comparison was made with the concentration of the lipoprotein components in individuals of the same age group of "normals" as established by Gofman and his co-workers. It was found that all but two of the cases fell within the range of "normals" established by Gofman. However, the clearing properties of heparin are confirmed, even in those cases with low resting levels. The clinical significance of these findings will be discussed.

21. The Diabetic Triopathy

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The association in the same individual of a series of sequelae consisting of neuropathy followed by retinopathy and nephropathy occurs particularly in diabetes with onset early in life and of peculiar severity. In the series of 75 patients studied, the types of neuropathy have included a typical so-called peripheral neuritis characterized by severe pain in the legs, loss of reflexes, muscle atrophy, increased protein in the cerebral spinal fluid, the diabetic diarrhea, especially of the nocturnal type with incontinence, or the so-called Charcot joints. The

retinopathy has been characterized by a malignant progression from an early stage with small capillary aneurysms to the retinitis proliferans. The neuropathy has been characterized by the occurrence of Kimmelstiehl Wilson lesions but also by arteriolarsclerosis, atherosclerosis and varying degrees of pyelonephritis.

Factual data bearing on the association of these lesions with changes in the serum lipoprotein and serum cholesterol are reported.

22. The Biologic Variability of Human Serum Beta Lipoproteins and Total Cholesterol in Late Maturity and Old Age

Donald M. Watkin, Eleanor Y. Lawry, and George V. Mann

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Sixty-three institutionalized men aged 47 to 92 were selected for study on the basis of age, cholesterol or S_f 12–20 levels and freedom from diseases known to be associated with disturbed lipid metabolism. No exclusions were made for clinical stigmata secondary to atherosclerosis. The diet was restricted to low cost institutional fare. Fasting blood samples were drawn from each individual twice weekly for ten weeks. Serum was analyzed for S_f 12–20, S_f 21–35, and S_f 35–100 beta lipoprotein molecules in the ultracentrifuge and for total cholesterol by the method of Abell. The serum of 34 subjects was divided in the clinic and the aliquots analyzed without identification of duplicate pairs. Estimates of the biologic variability of these serum constituents were derived from values for overall and technical variability.

Mean serum levels of all lipid fractions did not vary significantly between age groups. Biologic variability did not change with age from the sixth through the tenth decade. Technical error increased with mean level in all fractions studied. Biologic variability of beta lipoproteins but not that of cholesterol increased with mean level. The data indicate the necessity of considering the range of variability of beta lipoproteins and cholesterol in the interpretation of values obtained from single or a limited number of blood samples from a given individual.

23. The Serum Lipids and Serum Uric Acid in Normal Men and Women Past the Age of 65 Years

Menard M. Gertler and Bernard S. Oppenheimer

The Home for Aged and Infirm Hebrews of New York City

The serum lipids (serum free cholesterol, esterified cholesterol, neutral fats, lipid phosphorus, total lipids and S_f 10–20 molecules) and serum uric acid were determined in a group of 38 normal men and 91 normal women whose average ages were 77 years and 75 years respectively. The serum lipids were significantly higher in the women than in the men in all instances except neutral fats in which there was only an absolute higher difference. On the other hand the average value of serum uric acid was significantly higher in the men than in the women. These observations are at variance with the currently held views that men present atherosclerosis with greater frequency than women because men possess higher serum lipid values. In this age group women show higher serum lipid values and yet do not appear to present more atherosclerosis than the men.

Several facts were brought to light: (a) In the men of this age group the serum total cholesterol decreased with increasing age while in women the serum total cholesterol increased with age; (b) the S_f 10–20 molecules remained stationary in men but rose with increasing age in the women, (these observations extend views promulgated by Gofman); and (c) the serum S_f 10–20 molecules and serum total cholesterol

were significantly correlated in men but not in the women, the correlation coefficients being $+0.59 \pm 0.15$ and $+0.21 \pm 0.12$ respectively. It appears that the serum lipids may not be as important in atherosclerogenesis in women as in men.

The serum uric acid levels were significantly correlated with the serum lipids such as total cholesterol, lipid phosphorus and S_f 10–20 molecules in the men but not in the women. This is of particular interest because of the known association of gout and maleness, maleness and atherosclerosis, and gout and vascular disease. The interrelationships between serum lipids, serum uric acid and the possible association with atherosclerosis appear to be significant.

24. Analysis of Juvenile Atherosclerosis

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In pursuance of our belief that emphasis must be shifted from disease to lesions—and particularly to early, possibly reversible lesions—before real progress can be expected, we have analyzed the aortas of 60 consecutive cases in the age group 1 to 17 years that came to autopsy in a large general hospital and have compared the lesions with those in a smaller group of aortas of patients in the same age group obtained from the Coroner's Office with the following results: (1) A comparison of the results obtained from the two sources indicated that the terminal illness had nothing to do with the presence or absence of aortic lesions. (2) Every case beyond the age of 3 years had one or more focal deposits of material which was visible on the intimal surface after staining with Sudan IV. (3) Gross Sudan staining quadrupled the chances of finding minimal lesions. (4) The lesions were qualitatively similar but there were topographic and quantitative differences by age, sex, race and principal cause of death that may prove significant. (5) The failure to find a single typical pearly plaque in this age group might indicate that a hormonal factor or a "cessation of growth" factor must come into the picture before pearly plaques and disease ensue.

25. Cholesterol and Vascular Responses to Induction of Coarctation of the Aorta in Chicks

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These studies were undertaken to determine the effect of changes in the stream-lines of flow on the blood vessel wall. A tuck was placed in the aortic arch of 30 chicks, reducing the lumen by as much as 50 per cent. Three weeks later the plasma cholesterol of these animals was increased above that of unoperated chicks. On normal mash diet: the plasma cholesterol averaged 150 mg. per 100 cc. in the operated chicks, while it averaged 100 mg. per 100 cc. in the controls. On a 2 per cent cholesterol diet: the operated chicks averaged 925 mg. per 100 cc., while the appropriate unoperated controls averaged 445 mg. per 100 cc.

Changes in the uninjured aorta wall were of considerable interest. At a point beyond the tuck the following changes were seen: proliferation of intimal loose connective tissue (non-inflammatory) with the formation of a sub-endothelial cushion arrangement of fibroblasts in parallel rows oriented with reference to the blood stream. Sudan stains revealed marked fatty infiltration in the media and intima above and below the cushion, while there was no fat at the level of the cushion itself. Above the constriction marked plaque formation and atherosclerosis were present. At the site of narrowing the intima was free of plaques. Below the narrowing, fat deposition and atherosclerosis was present in a stream-line pattern. At a

point just beyond the constriction, craters (systolic pockets?) were noted in the intimal wall. Blood pressures above the constriction were in the normal range; pressures were markedly decreased distal to the constriction.

These data support the concept that fatty materials *filter* through the intima on the basis of filtration pressures. They provide evidence that vascular architecture is secondary to hydrodynamics. They indicate that a disturbance in aortic flow patterns may bring about marked changes in cholesterol regulation.

26. A Comparison of Morphologic and Chemical Methods of Grading Coronary Arteriosclerosis

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This report is concerned with our attempts to improve the present method of assessing the degree of coronary sclerosis in human autopsy material. In the past coronary sclerosis has been assessed by purely morphologic methods. At the best they are semiquantitative, the results vary considerably with different examiners, and they offer little information about the various factors that may be responsible for stenosis of the coronary lumen. In particular, they often fail to distinguish clearly between predominantly atheromatous, calcific or sclerotic thickenings of the arterial wall.

The degree of coronary sclerosis in 52 fatalities among middle-aged and elderly veterans has been assessed by a standard morphologic procedure (Davis and Klainer); and the coronary arteries have then been analyzed chemically for the amount of atheroma (total lipid content), the amount of calcification (calcium and phosphorus content), and the amount of sclerosis (total protein content). The results show a fairly good agreement between the morphologic and chemical methods when the series is taken as a whole; but there are wide variations when cases are analyzed individually. Each of the three tissue components is increased significantly in cases of marked coronary sclerosis, but the difference is particularly impressive in regard to the minerals. The results are to be reported in detail, and criticisms and suggestions on the methods and interpretations invited.

27. Lipoprotein Studies on Humans Subjected to Controlled Dietary Regimens with Subtraction and Addition of Fats, Sitosterol, and Dihydrocholesterol

Edwin Boyle, Charles F. Wilkinson, Jr., Raymond S. Jackson, and Martin R. Benjamin

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This report concerns the serum lipoproteins of a group of patients with xanthomatosis, angina pectoris, nephrosis, or a combination of these conditions. These patients were placed in a metabolic unit and studied serially during the four periods described below. They were always in nitrogen balance, with no significant weight change. (1) The subjects received a diet adequate in protein, minerals and vitamins but containing less than 1 Gm. of fat per 24 hours; (2) the diet was kept isocaloric and isonitrogenous and 52 Gm. of vegetable fat per day was added; (3) the above diet (2) was kept constant and 15 Gm. of sitosterol was added daily in divided doses with meals; and (4) patients were discharged from the metabolic unit, returned to a diet of choice and the sitosterol was either maintained at the above level or increased. During this time serum was analyzed for lipoprotein constituents in the analytic ultracentrifuge using a solvent density of 1.21. Preliminary results indicate that there is no sustained or marked reduction of the lipoproteins in the serum during the study although

during study period (1) there was an initial drop followed by a return to pretreatment levels after a varying period of time. These results may be explained by Gould's observation that the reduction of cholesterol intake results in its increased synthesis.

28. The Effect of Varying the Intake of Dietary Fat and the Ingestion of Sitosterol on the Lipid Fractions of Human Serum

Chas. F. Wilkinson, Jr., Edwin Boyle, Raymond S. Jackson, and Martin R. Benjamin

Department of Medicine, New York University Post-Graduate Medical School; the Fourth Medical (NYU) Division, Bellevue Hospital, New York, N. Y.; and the Laboratory of Metabolism National Heart Institute, Bethesda, Md.

A group of patients with xanthomatosis, angina pectoris, nephrosis, or a combination of these conditions, was placed in a metabolic unit and studied during the four periods described in the preceding abstract (Boyle, Wilkinson, Jackson and Benjamin). During this time, serum was analyzed three times weekly for free and esterified cholesterol, lipid phosphorus, and esterified fatty acids. All stools and urines were collected. The stools were analyzed for their sterol content; the urines for nitrogen and creatinine. These subjects maintained nitrogen balance and experienced no significant weight changes.

The total cholesterol tended to decline in period 1, but to a variable degree. In several, these values began to rise again after 10 days of the low fat diet, despite its continuation. The response to the addition of fat in period 2 was difficult to interpret because of this. During periods 3 and 4, the use of sitosterol did not yield the dramatic results reported by others. During the entire study, the percentage of esterified cholesterol remained constant. Fasting neutral fat levels likewise varied little except in a nephrotic, all of whose lipids declined during period 1. The phospholipid-free cholesterol ratio and stool sterol studies will also be discussed.

29. Effects of Heparin on Plasma Lipids in Normal Persons, and in Patients with Coronary Atherosclerosis, Nephrosis and Primary Hyperlipemia

Joseph Herzstein, Chun-I Wang, and David Adlersberg

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A comparison was made of the effect of intravenously injected heparin on plasma lipid partition and plasma clearing in 10 normal men, 5 patients with coronary atherosclerosis, 7 patients in the nephrotic state of nephritis and 3 with idiopathic hyperlipemia. Blood samples drawn before heparin administration and 15, 60 and 120 minutes later indicated an appreciable reduction in plasma total lipids, primarily in neutral fat content. Plasma cholesterol, esterified cholesterol and phospholipid fractions were unaffected.

In five normal subjects the mean fasting plasma neutral fat content of 315.4 mg. per 100 ml. was reduced by 20.7 and 33.5 per cent after 15 and 60 minutes respectively. In five normal individuals with induced alimentary lipemia the initial mean level of 283.2 mg. per 100 ml. was reduced by 31.7 per cent 15 minutes after heparin, an amount larger than one would attribute to physiologic fat clearance in this brief interval. In five patients with coronary atherosclerosis, whose mean fasting plasma neutral fat level was 386.2 mg. per 100 ml., heparin injection was followed by a fall in neutral fat of 22.6, 14.3 and 24.7 per cent after 15, 60 and 120 minutes, respectively. A group of patients with nephrosis with a high mean fasting plasma neutral fat content of 838.2 mg. per 100 ml. showed, following heparin, a fall of 12.8, 18.1 and 24.8 per cent after 15, 60 and 120 minutes, respectively. In this group an increase in size of dose of heparin effected a somewhat greater reduction in plasma neutral

fat content. In three patients with idiopathic hyperlipemia with unusually high plasma total lipids, up to 2090 mg. per 100 ml., varied doses of heparin effected a large and rapid reduction in neutral fat. In this group the per cent fall in neutral fat within a two-hour period after heparin ranged from 23.9 to 60.3 per cent.

As measured by light transmission, plasma opacity or turbidity was reduced after heparin injection in all groups, but to a variable degree. Plasma of normal subjects, and especially that of normal men with induced alimentary lipemia, cleared to a greater extent than plasma of patients in the other three categories. Fasting plasma of patients with nephrosis and essential hyperlipemia, usually opaque before heparin injection, cleared least of all. In the nephrotic group an increase in dosage of heparin did not affect plasma lactescence.

Light transmission of plasma was associated only in a general way with its lipid content. In patients with nephrosis and essential hyperlipemia, plasma clearing induced by heparin seemed unrelated to the observed fall in neutral fat.

30. Hypocholesterolemic Effect of a Brain Fraction in Patients with Elevated Serum Cholesterol

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Fourteen patients with clinical manifestations of arteriosclerotic heart disease whose serum cholesterol levels had been elevated for periods up to one year were selected for an oral administration of a cholesterol-free, lipid-poor residue of beef brain. Each patient was advised to stay on his usual diet and to take 6 Gm. of the material daily, in four divided doses. Weekly serum cholesterol determinations were made before, during, and after the course of brain powder. After two weeks the dose was raised to 40 Gm. per day for two more weeks, when tolerated. The smaller dose of brain powder did not cause a significant lowering of serum cholesterol in most cases. In the six patients who were able to tolerate the larger amount of material, only three showed a definite reduction of serum cholesterol below the control levels, but two of these attained levels lower than any noted in the previous year. The latter two also had a prompt rise in serum cholesterol on withdrawal of the agent, and the effects of both administration and withdrawal could be repeated.

This substance, first shown to be active in cholesterol-fed chicks, has been shown to work similarly in rats, mice, and now humans with varying degrees of effectiveness. The failure of response in some of the patients could have been due to poor cooperation, inasmuch as the sheer bulk of material acted as a deterring factor. The mechanism of action is not clear, but may be largely due to conversion of intestinal cholesterol to coprosterol. Further purification and isolation of the active principle, as now in progress, will perhaps provide a more effective and tolerable hypocholesterolemic agent.

31. The Effects of Smoking and of Nicotine on the Ballistocardiograms of Normal Subjects and Patients with Coronary Artery Disease

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In an attempt to increase the diagnostic value of the ballistocardiograph in the detection of coronary artery disease, the response to cigarette smoking of normal persons and of patients with angina pectoris or remote myocardial infarction was investigated. Two hundred persons were subjected to a cigarette test. This test consisted of the recording of a resting

ballistocardiogram and electrocardiogram, after which the subject smoked a standard brand cigarette. Both immediately and five minutes after smoking ballistocardiograms and electrocardiograms were repeated. The ballistic response was graded negative, borderline, or positive. A negative test signified no significant alteration from control. A test was considered positive if the majority of complexes showed definite deterioration, and borderline if there were deterioration of only expiratory complexes.

Six and eight tenths per cent of the normal subjects showed a positive response. All of these were male, and half over the age of 60. Of the group with clinical coronary artery disease 58.6 per cent had positive tests. This discriminatory ratio of 9:1 between patients and normal persons exceeded that obtained by any other objective procedure studied by us.

In order to verify the role of nicotine as the responsible agent in this test, 10 subjects were given 0.5 mg. of nicotine base sublingually, and the ballistic alterations were compared with the changes obtained after smoking. Sufficient similarity of response was present to justify the conclusion that nicotine was in large measure the basis of the alterations observed.

The precise mechanism through which nicotine acts to produce ballistic abnormality and the reason for the selectivity of its action in patients with coronary artery disease are not yet clearly understood, but work bearing on these points is in progress. Consideration is being given to the possible role of pitressin-induced coronary vasoconstriction in producing the nicotine effect.

32. The Diagnostic Value of Serum Cholesterol Determination, Ultracentrifuge Studies and Chylomicron Levels in Fasting Serum

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The report deals with one phase of a long range multiphasic project on the physical and chemical makeup of serum lipoproteins. The clinical material consists of 100 patients with unequivocal evidence of myocardial infarction and 197 subjects considered as controls. Out of that series 33 cases chosen at random form a group of atherosclerotics with ultracentrifuge studies, serum chemistry studies and chylomicron levels (percentage of lipoprotein particles 0.3 micron in diameter and larger) performed in fasting condition. The uniformity of methods and conditions is emphasized. The distribution curves (a similar approach to that of Gofman and associates) have been worked out for total cholesterol and chylomicron levels. Statistical comparison was made to ascertain the diagnostic value of the three tests by comparing the values obtained with those of "normals" and with those of myocardial infarction victims. The method used consisted of tabulating the number of cases according to the percentage of "normals" and myocardial infarction patients a given case exceeds. In relation to "normals," chylomicron levels, cholesterol, and ultracentrifuge results appeared of diagnostic value in the order mentioned. When the cases were grouped, comparing them with the similar myocardial infarction population, all three tests have approximately similar diagnostic value. A mutual complementation of tests in a multiple approach to atherogenesis will be discussed.

33. Coronary Artery Lesions in Sudden Death

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The coronary arteries of 100 adults who died suddenly of coronary artery disease and 75 controls have been examined by a clearing technic. Perfusion and fixation of the vessels is carried out prior to dissection of the major arborizations from the heart. Decalcification,

dehydration and clearing precedes examination with the dissecting microscope. Cross sections are made and embedded for microscopy. The experimental group includes adults below 60 without extracardiac cause of death at autopsy. Cases are eliminated with microscopic lesions responsible for death in tissues other than the coronary arteries. The control group comprises individuals of similar age, sex, and race dead of causes other than coronary artery disease. Hemorrhages within atheromatous or fibrous plaques of the coronary arteries occur in almost all cases of the experimental group. The hemorrhages are usually multiple and vary in age from fresh extravasations to areas of iron-containing pigmentation. All major branches are involved and the hemorrhages are usually nonocclusive. Thrombi are frequently associated with older hemorrhages but not with fresh ones. Fresh mural hemorrhages are not observed in controls. The preponderance of mural hemorrhages in white males and the uniform incidence of cases within the fourth, fifth and sixth decades is discussed.

34. Effect of Cholesterol on Antilipfanogen and Lipfanogen Levels in Vitro

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The addition of colloidal cholesterol to tissue culture media containing known levels of antilipfanogen and of lipfanogens, results in a lowering of the free antilipfanogen and *a liberation of free lipfanogens*, with consequent increase in the deposition of stainable fat. The evidence indicates that free cholesterol combines with the antilipfanogen, thereby reducing the ability of this substance to curtail the fat-depositing action of the lipfanogens.

35. Serum Lipid and Protein Fractions. IX. Comparisons of Ninety-Six Patients with Vascular Disease and Sixty Normal Controls (with Additional Notes on Blood Donors)

Irving Leinwand and D. H. Moore

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Ninety-six cases made up of eight types of disease where atherosclerosis is common were studied. Mean figures on the lipid and protein determinations are presented for each group. Many individuals were studied with multiple determinations for as long as three years. Comparisons are made with normal sera from healthy personnel and patients without obvious disease. The importance of the selection of proper normal controls is emphasized by the findings in two groups of professional donors accepted for transfusion at two different blood banks. These bloods showed a significant decrease in albumin and an increase in gamma globulin. These again are compared with the normal controls used in this series. Two types of buffers were used in the electrophoresis for technical purposes of comparison. In cases of arteriosclerosis obliterans those patients with a hyperlipemia or hypercholesterolemia had a higher beta globulin than patients without hyperlipemia. In thromboangiitis obliterans the level of the serum lipids had no relationship to the amount of beta globulin since the beta globulin was slightly elevated to the same extent regardless of whether hyperlipemia was present or not. In xanthomatosis the beta globulin was highest and was usually accompanied by a slight increase in the gamma globulin. The other cases studied showed variations which will be discussed. Statistical analysis of these results will be presented.

DEMONSTRATION

CHROMATOGRAPHIC PARTITION OF SERUM PROTEINS, PROTEIN-BOUND LIPIDS, AND PROTEIN-BOUND CARBOHYDRATES IN RABBITS, BEFORE, DURING, AND AFTER CHOLESTEROL FEEDING

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All these values are far more stable and uniform in rabbits than in human beings. Changes during feeding are still erratic, and we are not yet able to determine from the elpherograms the point at which anatomic lesions might develop.

36. FURTHER STUDIES OF HUMAN CIRCULATING PLASMA HEPARIN LEVELS—CORRELATION WITH SERUM LIPIDS AND LIPOPROTEINS

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Heparin levels were determined using the anticoagulant method of assay previously reported. Determinations were made in duplicate with the technicians unaware of the previously determined clinical diagnosis. The results indicate that there is a tendency for circulating heparin to decrease with age. Serum lipoproteins of the S_f 12–100 class correlate well inversely with plasma heparin. When the total cholesterol level and S_f 12–100 lipoproteins do not parallel each other, the heparin level shows no relationship to the total cholesterol but has a positive inverse correlation with the S_f 12–100 lipoproteins. The results indicate that heparin deficiency may well be a factor in the accumulation of abnormal amounts of these lipoproteins.

Heparin levels of 50 patients who had previously had a myocardial infarction were compared with 50 controls matched as to age, weight and sex. Although there was some overlap, in general plasma heparin was lower in the coronary group.

37. PENTAPYRROLIDINIUM (M & B 2050) IN THE TREATMENT OF SEVERE HYPERTENSION

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Previous experience in this clinic indicated that, because of marked variability in absorption, hexamethonium administered orally was unsatisfactory for the routine treatment of hypertension. Twenty severely hypertensive patients have been treated for periods ranging between one and three months with the new ganglionic blocking agent, pentapyrrolidinium (M & B 2050). Prior to any treatment 10 had grade IV, 6 grade III, and 4 grade II hypertension (Keith, Wegner, and Barker). All except four had been under previous therapy with parenteral hexamethonium usually supplemented with oral Apresoline. In all instances blood pressure levels have been recorded in the home four or more times daily.

After regulation with M & B 2050 orally as the only medication the average levels of blood pressure have been lower than on previous regimens in 18 of the 20 cases. Because of the long duration of action dosages administered at eight-hour intervals produced a persistent reduction of blood pressure with fewer periodic elevations as compared with hexamethonium. Responses have been far more uniform from day to day than with hexamethonium. Effective total daily dosages have varied between 0.4 and 2.0 Gm.

Constipation has been less pronounced after M & B 2050 than after hexamethonium and usually can be controlled readily by 15 to 30 mg. of prostigmine orally once daily. The other

side effects of ganglionic blockade have been similar to those produced by hexamethonium including loss of visual accommodation, dry mouth, impotence and postural hypotension. In addition, individual regulation of each case is required. Nevertheless, these early results suggest that oral M & B 2050 provides a more predictable, more prolonged and better tolerated hypotensive response than does hexamethonium.

38. Some Observations on the "Clearing" of Artificial Emulsions Induced by Pre- and Postheparin Serum from Normal and Diabetic-Atherosclerotic Subjects

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Two tenths cc. postabsorptive serum, obtained before and 10 minutes after 25 mg. intravenous heparin, was added to 1.0 cc. dilute mineral oil (MO) or olive oil (OO) emulsion and optical density (OD) read in Coleman Jr. Spectrophotometer at 600 μ immediately on mixing (OD zero) and after two and one-half hours (OD-2½). Decrease in OD denotes "clearing." Abnormal serum plus 1:250 water dilution MO gave significantly ($p < .001$) higher OD-zero value than normal serum. Normals showed clearing in pre- and postheparin specimens not noted in abnormals. With 1:500 MO normals showed no significant clearing, although clearing was greatest in postheparin specimen. Abnormals showed less clearing than normals, except the diabetic-infarct group which showed greater clearing in both pre- and postheparin specimens ($.001 < p < .01$). With 1:250 olive oil normals showed no significant clearing in pre- or postheparin samples, but significant clearing occurred in abnormal group. Serum clearing property shows daily variation in individual normal subjects. pH of serum OO mixture (8.2 ± 0.2) did not change significantly with clearing and clearing was not improved by pH adjustment either way. Comparing clearing of MO-saline and MO-water plus serum reveals marked clearing inhibition by saline.

39. Revascularization of the Myocardium by Cardiopexy in the Treatment of Coronary Artery Disease

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The aim of all surgical procedures for the treatment of coronary artery disease is to increase the blood flow through existing coronary channels or to increase the anastomotic circulation from extracardiac sources. Cardiopericardiopexy with talc converts an ischemic myocardium into a hyperemic one by the introduction of a foreign body (magnesium silicate) into the pericardial sac, thus creating a foreign body reaction with the ultimate production of a chronic generalized granulomatous pericarditis. As a result of a study of the clinical results obtained in 47 patients with severe coronary insufficiency during the past four years, this operation is considered the best available for increasing coronary collateral circulation, because of its simplicity, reasonable safety and beneficial results.

The operation has been performed in 47 patients with coronary sclerosis who were completely disabled or markedly limited in their activities because of anginal pain or congestive failure. The period of follow-up has ranged from four months to four years. The clinical results have been classified as excellent in 19 patients and good in 14. In seven patients the follow-up has been too short for evaluation. Three patients died during or soon after the operation and four patients have died during the follow-up period. Most of the patients were able to resume normal or only slightly curtailed physical activities without angina, dyspnea or fatigue.

40. Fat Loading Studies in Relation to Age

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Two groups of hospitalized subjects, one with a mean age of 24.9 years, the other an older group with a mean age of 62 years, were given fat-loading tests with a view to uncovering any possible age difference in reaction to alimentary lipemia. None of the individuals was known to have any metabolic disease or any stigmata associated with atherosclerosis.

Fasted subjects were given a test meal consisting primarily of 40 per cent sweet cream, measured in relation to their weight, in the proportion of 1 Gm. of fat to 1 Kg. of body weight. Chemical determinations were made for total lipids and lipid fractions on the fasting sera and for serum total lipids on specimens obtained 2, 4, 6, 12 and 24 hours after the test meal.

The mean value for fasting total lipids in the young group was 638 mg. per 100 ml. while that of the older group was 809.1 mg. per 100 ml. After two hours the mean rise in total serum lipid for both groups was the same. The concentration of total lipids in the serum in the young group fell almost to the fasting level by the sixth hour, while at the four and six hour periods the older group still showed elevated postprandial lipid levels. An elevated serum total lipid content persisted for the 24 hour period in the older group. A small group of six normal ambulatory subjects with a mean age of 50.3 years, in whom the tests were continued for a six-hour period only, resembled the young group in its behavior, the alimentary lipemia having cleared by the fourth hour.

Whether the prolonged postprandial lipemia is indicative of a faulty lipid metabolism in the old and, if so, whether it represents a predisposing factor for atherosclerosis is unknown at present.

41. Hyperbeta-globulinemia Connected with Hypoalbuminemia in Arteriosclerosis and Coronary Sclerosis

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Electrophoretic studies of serum protein were performed on 30 arteriosclerotic men and 30 women, and also on 20 men with coronary disease. It was found that these subjects have a higher beta-globulin ratio than the non-arteriosclerotic group, and that hyperbeta globulinemia was, in almost all instances, accompanied by hypoalbuminemia. The deviations from the normal average were more striking the closer was the occurrence of the coronary occlusion. The discussion will include some correlations between arteriosclerosis and protein metabolism according to recent concepts.

42. The Effects of Specific Steroids and Phosphatides upon the Levels of Plasma Lipids

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As previously noted, the administration of large amounts of fat of vegetable origin to normal and abnormal individuals results in a consistent depression of the plasma levels of cholesterol and phospholipids. The present study deals with the evaluation of effects of a variety of sterols and phospholipid material of vegetable origin upon the plasma lipids of patients with advanced diabetic vascular disease under quantitatively constant conditions. To date, the findings indicate that several of such substances have some significant effect under specific experimental conditions. The most impressive to date has been obtained with a mixture of lecithin-cephalin derived from soy.

43. Diffusion Coefficients of Some Gases and Nongaseous Solutes in Human Arterial Tissue

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Determinations were made in vitro of the diffusion rates of oxygen, carbon dioxide, nitrogen, glucose, lactate and iodide through the human aortic wall. The measurements were carried out under sterile conditions on preparations of the aortic intima (with attached subintimal tissue) and media, using the diffusion apparatus described by S. G. Johnsen and J. E. Kirk (Circulation **4:** 478, 1951). The average diffusion coefficients* observed for the aortic intima were: oxygen 0.00068 (s.d. 0.00024, N = 12), carbon dioxide 0.00046 (s.d. 0.00017, N = 12), nitrogen 0.00065 (s.d. 0.00017, N = 10), glucose 0.00010 (s.d. 0.00004, N = 6), lactate 0.00013 (s.d. 0.00006, N = 5), and iodide 0.00023 (s.d. 0.00005, N = 5). For the aortic media the corresponding values were: oxygen 0.00063 (s.d. 0.00022, N = 11), carbon dioxide 0.00038 (s.d. 0.00014, N = 12), nitrogen 0.00062 (s.d. 0.00015, N = 11), glucose 0.00009 (s.d. 0.00003, N = 5), lactate 0.00010 (s.d. 0.00003, N = 5), and iodide 0.00021 (s.d. 0.00008, N = 6).

* Diffusion coefficient: Units of the substance diffusing through 1 cm.^{2} of the membrane in one minute at a concentration gradient of 1 unit per ml. per cm.

44. Serum Lipid and Protein Fractions. VII. Lipid Transport in the Human as Determined by Electrophoresis of the Proteins

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Approximately 1500 electrophoretic determinations of the serum proteins were made on 300 individuals. The present series of reports comprises a summary of four years of study of the electrophoretic pattern of the proteins before and after cold ether extraction in an effort to afford a reasonable correlation of laboratory data regarding lipid transport in so-called normal and abnormal individuals. A chart is presented to show the differences in reaction of the electrophoretic pattern between the 60 so-called normals, 90 patients with a disease where atherosclerosis is common, and 150 patients with other diseases. The mean determinations in the 90 patients show a correlation of an increase in the beta globulin and increased lipid. This increase is also associated at times with an increased gamma globulin. The alpha 2 globulin was increased in three cases of acute myocardial infarction where the blood was taken while the patients were in shock. These three patients died. Ordinarily an increase in alpha 2 globulin is associated with a febrile disease. In 150 patients in various disease groups not particularly associated with lipid disturbances, there were variable increases in gamma globulin. In all disease there is a variable decrease in albumin. The alpha 1 globulin remains fairly constant.

45. Serum Lipid and Protein Fractions. VIII. The Variability of the Pattern of the Lipid Protein Relationship

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While the amount of lipid estimated by chemical analysis may not vary too much from month to month, the amount of lipid associated with each protein component separated by electrophoresis varies considerably. It appears that the most constant amount of lipid associated

with a protein fraction is with the beta globulin, in sera with normal or increased lipids. The decrease in the beta globulin component measured by electrophoresis after cold ether extraction is from 50 per cent to 75 per cent. Thus this fraction sustains the greatest loss in percentage. However, lipids are associated with all of the protein fractions. In fact, the albumin and gamma globulin are associated with at least half of the lipid in the serum. This is easily calculated and demonstrated by estimating the loss in pattern area following cold ether extraction. This variability of the lipid/protein pattern appears to be more pronounced in disease states regardless of the type of disease. There does not appear to be any difference in the lipid/protein pattern as determined by electrophoresis between males and females, except for the pregnant female where the lipid content of the serum is definitely elevated.

46. Serum Lipid and Protein Fractions. X. The Electrophoretic Pattern and Lipid Relationship in Some Experimental Animals and Man

Irving Leinwand and Dan H. Moore

New York University–Bellevue Medical Center, St. Clare's Hospital, and College of Physicians and Surgeons, Columbia University, New York, N. Y.

A group of 40 mice were subjected to stress in the form of fasting for 12 hours, and the electrophoretic patterns of the sera of these animals were compared with a control group of 40 nonfasting mice. This experiment was performed with a group of both younger and older mice. In both groups there was more ether extractable material present in the sera of the fasting animals. Hypophysectomy in rats produced the same phenomena. In humans the effect of fasting was difficult to duplicate because of variability in the patient himself. However, the difference in fasting and nonfasting specimens in regard to ether-extractable material was apparent in specimens separated by long intervals. Specimens taken during fasting and repeated from one and one-half to four hours after eating showed little change in protein, fatty acids, lipid phosphorous, total cholesterol, or ether extractable material. These results did not appear to be different in patients with normal or abnormal lipids. There did not appear to be any difference between males and females except in fowl. In fowl there appears to be more sex difference in the electrophoretic pattern than in any other animal. The possible significance in relation to experimental data will be discussed.

47. Effects of Ovariectomy on Experimental Atherosclerosis in Rabbits

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In an attempt to assess the influence of endogenous ovarian secretion on experimental cholesterol-induced atherogenesis, a comparison was made of intact and ovariectomized rabbits. The two groups of rabbits exhibited the following findings in response to a cholesterol-supplemented diet (0.5 Gm. cholesterol + 5 cc. olive oil daily) fed for 50 days: (1) similar patterns of feed intake and weight gain; (2) similar levels of hyperphospholipemia and hypercholesterolemia; (3) more marked aorta and coronary atherogenesis in the intact than in the ovariectomized group.

It is concluded that endogenous ovarian secretion of the intact female rabbit has no suppressing influence on experimental cholesterol-induced atherogenesis in either the aorta or the coronary vessels.

48. Interrelationships between Plasma Lipids and Atherosclerosis in Residents of a Home for the Aged

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Since plasma lipid patterns have been implicated in the pathogenesis of human atherosclerosis, a study was undertaken on the interrelationships among plasma total cholesterol levels, total cholesterol/lipid phosphorus (C/P) ratios and atherogenesis (aorta and coronary) in 120 residents (48 men, 72 women) of a home for the aged.

Eight subjects (4 men, 4 women) had no clinical evidence of either coronary or aorta atherosclerosis (group 1). Thirty-five patients (15 men, 20 women) exhibited evidence of aorta involvement without coronary involvement (group 2). Seventy-seven patients (29 men, 48 women) had clinical atherosclerosis of both the aorta and coronary beds (group 3). Thus there was no demonstrable sex difference in incidence of atherosclerosis in the male and the female at this age (mean age: men 78.7, women 78.4). The three groups had similar plasma lipid patterns, that is, there were no demonstrable differences among them in plasma total cholesterol level or C/P ratio. Thus no correlations were demonstrated in this study between plasma lipid patterns and atherogenesis in older people. Within each group, plasma total cholesterol levels were higher in the females than in the males; in contrast, the two sexes had similar C/P ratios throughout. No males were seen with plasma total cholesterol levels in excess of 260 mg. per 100 cc., whereas several females had values over 300 mg. per 100 cc. Thus a sex difference was observed in plasma cholesterol levels in the aged, unassociated with any clinically demonstrable sex difference in atherogenesis.

49. Enteric Factors in Cholesteremia and Atherosclerosis

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We have previously reported that addition of an aluminum hydroxide gel to the diet of chicks inhibits or delays the production of hypercholesteremia and atherosclerosis. Attention has since been called to a number of other dietary constituents which also can influence cholesterol regulation and the secondary effect on blood vessels. We have continued our studies, using Aureomycin, cholesterol acetate and soy sterols. The effect of intermittent cholesterol diets has also been studied.

Addition of Aureomycin to the diet in amounts used commercially to enhance fattening had no significant effect on the plasma lipid levels or on atherosclerosis. Addition of cholesteryl acetate (1 per cent) to the diet intensified the degree of hypercholesteremia and atherosclerosis exactly as if an equivalent amount of free cholesterol had been used. Crude soy sterols (1.3 per cent) added to the diet effectively reduced the plasma cholesterol and degree of aortic and coronary atherosclerosis.

The effect of dietary regimens utilizing alternate weeks of cholesterol feeding and experimental regimen have also been studied. A summary of the data utilizing the various regimens is given in the accompanying table. All these animals were fed a diet to which 1 per cent cholesterol and 5 per cent cottonseed oil was

	Plasma Cholesterol mg. %	Atherosclerosis		
		Aortic		Coronary Vessels involved
		Incidence*	Degree	
1% Cholesterol throughout	743	4/4	1.0	11%
Unloading regimens				
Regular Mash	117	6/12	0.4	1%
5% oil + Mash	121	3/5	0.5	1
Uncooked Rice	519	3/3	0.9	18
Soy Protein Alone	321	4/5	1.0	8
Sawdust Alone	390	4/5	1.3	4

* Numerator = number of chicks with lesions; denominator = total number of chicks.

added on the first and third weeks. The experimental regimen listed was given on the second and fourth weeks. Plasma cholesterol levels were obtained at the time of the sacrifice at the end of the fourth week.

The data in the table demonstrate that the pattern of cholesterol ingestion and the nature of the dietary regimen during the cholesterol-free period may markedly affect cholesterol regulation.

50. Observation on the Stability of Serum Lipids

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In a large series of serum lipid determinations, taken repeatedly on the same individuals, it was found that they showed various degrees of stability. It was often observed in high, low or normal findings that little change was produced by diet, lipotropic drugs or hormones. Conversely these same agents revealed marked changes under the identical conditions in another group of individuals. The pattern of stability usually becomes apparent after a few serum lipid determinations are taken. Therefore, these factors must be kept in mind when judging the effect of any modality. Also noted in this series was the fact that many who showed considerable variability in the beginning, especially in the lowering of total lipids and cholesterol by restricted diet, were eventually able to return to their former diet without elevating these factors in the serum, thereby showing a stabilization of the lipids.

51. The Surgical Treatment of Neurotrophic Plantar Ulcers in Arteriosclerotics

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These lesions are resistant to local and systemic therapy and are difficult to heal and maintain healed. The loss of sensation in the nerve distribution in which they occur is the result of pathologic changes in the nerve structure. As a rule these lesions begin insidiously in callus sites, progress without remission and invade subcutaneous tissue, fascia, tendon sheaths, joints and bone. Their chronicity favors excessive surrounding scar tissue formation which, in itself, impedes local blood supply and the reparative process. Numerous surgical procedures heretofore directed toward excision and plastic repair have not, as a rule, remained successful. In an attempt to increase blood supply, the only remaining available source seemed, to the author, to be the marrow cavity of the underlying bone. With this in mind, after bacteriologic study and local and systemic therapy with appropriate antibiotics in an attempt to control local infection, the ulcer has been excised, the cortex of the underlying bone removed and, in those cases where the marrow of exposed bone has had hemopoietic function, the granulations have subsequently filled the wound, the epithelium has become attached to them, and has proliferated and healed. A small series of these cases has been so successful that the process is presented for trial in other hands and for further evaluation.

52. Importance of the Effects of Heparin and Antiheparins on Lipemia

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In view of the increasing knowledge about the effect of heparin on lipoproteins (especially on those involved in the pathogenesis of arteriosclerosis) and about the lipemia clearing property of heparin, the basic question seems to be the following one. Are these effects physiologic, that is, do they occur in a normal organism? The answer to this question is not

quite clear yet, but the following experimental results may be of some value.

Alimentary lipemia can be cleared by the injection of heparin, yet during the physiologic disappearance of lipemia no clearing activity of the blood is detectable. Heparin-cleared lipemia can be brought back by the injection of protamine, but cannot be influenced by two other antiheparin substances, namely toluidine blue and neutral red. The explanation for these findings might be the fact that heparin has a larger affinity for the clearing factor precursor, than for toluidine blue, but in turn a larger affinity for protamine than for the clearing factor precursor. The latter statement is a conclusion based on the following experimental results. (1) When a mixture of heparin and toluidine blue is injected into a lipemic animal, the lipemia will be cleared, even if the ratio of heparin to toluidine blue is 2:100. Similarly, the presence of the clearing factor is demonstrable in normal (nonlipemic) dogs after such an injection. (2) A heparin-protamine mixture (in a 1:1.6 ratio) is not able to clear lipemia or to give rise to a clearing substance.

If protamine is injected into a lipemic dog (without previous heparin injection), a dramatic increase in lipemia occurs, which does not seem to be due merely to a direct heparin-neutralizing effect. This increase can be produced only when some visible lipemia is present in the blood. Once the lipemia has disappeared physiologically, protamine is not effective any more, although we found the thoracic duct very milky in these cases. Arginine, the most important constituent of protamine fails to have such an effect.

On the basis of the above experiments the conclusion is forthcoming that the affinity between heparin and clearing factor precursor is a very strong one. The effect of protamine on alimentary lipemia might be to bring back into the bloodstream the fatty substances which have been removed from the blood in the course of the physiologic fat metabolism, thus rendering the blood more lipemic. The significance of the latter phenomenon with regard to the development of arteriosclerosis is being investigated.

53. Effects of ACTH on Plasma Lipids and Atherogenesis in Cholesterol-Fed Chicks

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Since previous work from this department demonstrated that adrenal steroids may influence plasma lipid patterns and atherogenesis, a study was undertaken on the chronic effects of corticotropin in cholesterol-fed cockerels. In an initial experiment, the daily administration of 8 mg. corticotropin was without apparent influence. In a second study, 10 to 30 mg. daily of a long-acting corticotropin (ACTHAR GEL), were administered to cholesterol-fed cockerels for a seven-week period. The hormone accentuated hypercholesterolemia and hyperlipemia, without altering the plasma total cholesterol/lipid phosphorus ratio. The control and experimental groups exhibited a similar incidence and severity of both aorta and coronary atherogenesis. These effects of corticotropin are similar to those previously observed with hydrocortisone.

It is concluded that corticotropin, in doses adequate to stimulate the adrenal cortices of cholesterol-fed cockerels, accentuated hyperlipemia without affecting atherogenesis.

54. Failure of Vitamin E, Vitamin B_{12} and Pancreatic Extracts to Influence Plasma Lipids and Atherogenesis in Cholesterol-Fed Chicks

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Vitamin E (100 mg. per day) and vitamin B_{12} (15 μ per day) given orally or parenterally failed to influence plasma lipid patterns and atherogenesis in the aorta or coronary vessels of cholesterol-fed cockerels. Similar negative results were obtained with several oral pan-

creatic preparations (1 per cent in the diet)—Dragstedt's lipocaic (Lilly), lecithin (Associated Concentrates), pancreatin (Wilson, Armour), Chaikoff's antifatty liver factor (Lilly), activated whole pancreas (Viobin)—given to intact and depancreatized cockerels fed cholesterol. Negative results were also obtained with a parenteral pancreatic extract (Mulford).

These observations, extending previous negative results with choline and inositol, are further evidence for the lack of influence of lipotropic factors on experimental cholesterol-induced atherosclerosis in cockerels.

55. Atherosclerotic Stenosis of the Lower Abdominal Aorta

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The abdominal aorta is the most common site of atherosclerotic involvement. Narrowing of the artery to a point of complete occlusion is seen at the bifurcation or just above it. This condition begins to affect people during the fourth decade of life. The patient complains of cramps or pain in the leg muscles, weakness and, not infrequently, of a burning sensation of the feet. The pain and cramps may be precipitated by walking, although in most instances they occur while the patient is at rest, particularly during the night. Mild exercise, rubbing of the affected muscle or stamping of the feet on the floor offer various degrees of relief. On examination one finds in addition to the well-known general systemic signs and symptoms of atherogenesis (which will be reviewed) various degrees of asthenia of the leg muscles. In the advanced stages of the disease trophic changes of the skin of the feet, ulcers and manifestations of thrombotic gangrene may develop.

A special technic for surveying the abdominal aorta roentgenologically will be presented. It is most valuable in this condition since, in the majority of cases, it makes arteriography with contrast media unnecessary. Occasionally, in more complicated cases, arteriography may have to be employed to differentiate this disease from other intrapelvic conditions. The routine use of oscillometry is recommended.

The prognosis of atherosclerotic stenosis of the abdominal aorta is favorable, provided that intensive appropriate therapy is instituted. If the possibility of atherosclerotic stenosis of the abdominal aorta is kept in mind, the condition will be discovered before complete obliteration develops. As a rule these patients improve greatly. Some of our cases who were totally disabled and unable to walk more than 100 to 200 feet are gainfully employed at present and able to walk without discomfort for a mile and more. Trophic lesions heal and concomitant systemic manifestations of atherogenesis improve greatly. Clinical data in some of our cases are suggestive of the arrest of the general process of atherogenesis with improvement of the local process and various degrees of reversibility.

Cases will be reported in detail and therapy will be discussed.

ABSTRACTS

BACTERIAL ENDOCARDITIS

James, T. N.: Enterococcal Endocarditis. Arch. Int. Med. **90:** 646 (Nov.), 1952.

Two cases of successfully treated enterococcal endocarditis are presented, and penicillin and streptomycin are recommended as the antibiotics of choice. Intramuscular injections in the patient with enterococcemia should be kept at a minimum because of the organisms' proclivity for forming abscesses. This makes the intravenous route for penicillin administration more reasonable, particularly since experience has indicated the advisability of large doses of penicillin in this disease.

Use of an indwelling intravenous polyethylene catheter is recommended when prolonged intravenous therapy is planned. Dental infections are foci from which enterococcemia may originate and studies are now being carried out to determine how many of the bacteremias occurring commonly after dental extraction are due to Enterococcus.

BERNSTEIN

BLOOD COAGULATION

Engelberg, H.: Heparin Therapy of Severe Coronary Atherosclerosis, with Observations of Its Effect on Angina Pectoris, the Two-Step Electrocardiogram and the Ballistocardiogram. Am. J. M. Sc. **224:** 487 (Nov.), 1952.

The possibility of benefit accruing from the use of heparin in patients with coronary artery disease was suggested to the author by the reported changes in the serum transport phase of lipids following administration of this agent. A group of 29 patients with severe angina pectoris unresponsive to other therapy for periods of 6 to 12 months was selected. Heparin was given in 100 mg. dosage intravenously twice weekly for most of the observations. The anticoagulant effect of this dosage was not significan after six hours; there was no evidence of vasodilata tion. The results were favorable in 55 per cent of the patients treated, with marked relief of angina in a few. Improvement in exercise tolerance and in the two-step electrocardiogram was observed in 50 per cent of the patients examined by these methods after heparin therapy. Improvement in the ballistocardiographic records obtained after treatment was observed in about half of the patients. No serious reactions were observed following heparin administration. The author concludes that this agent will be useful in the prevention and treatment of atherosclerosis because of its effect upon the plasma lipoproteins.

SHUMAN

Ting, K. S., Livingstone, H. M., and Allen, J. G.: Effect of d-Tubocurarine on Blood Coagulation Time. Anesthesiology **13:** 594 (Nov.), 1952.

A study was performed on 25 dogs to determine whether or not d-tubocurarine altered blood coagulation time. The dose employed was 0.17 mg. per kilogram. On the basis of the results, it was concluded that this substance did not significantly affect the whole blood clotting time.

ABRAMSON

Wessler, S.: Studies in Intravascular Coagulation. I. Coagulation Changes in Isolated Venous Segments. J. Clin. Investigation **31:** 1011 (Nov.), 1952.

More than 75 years ago it was stated that a stationary column of blood in the vein included between two carefully applied ligatures will remain liquid for weeks. Because of the absence of details of this experiment, the work was repeated by preparation of an isolated venous segment of the dog. It was found that coagulation occurs far more slowly in

blood in contact with the endothelial-lined surfaces of isolated venous segments than in silicone-coated vessels or by other in-vitro technics. This holds true although the blood is completely stagnant. In this experiment it appears that a fibrin clot can develop prior to the disappearance of demonstrable amounts of prothrombin or the elaboration of measurable quantities of clot accelerators. This observation is of clinical significance since induced hypoprothrombinemia is currently employed to retard intravascular coagulation. It will be significant to ascertain whether such hypoprothrombinemia actually does cause a retardation in the fibrin deposition in vivo.

WAIFE

Triantaphyllopoulos, D. C., and Waisbren, B. A.: Lack of Influence of Penicillin on Blood Coagulation. Arch. Int. Med. **90:** 653 (Nov.), 1952.

Experiments were done in vitro and in vivo on the effect of varying concentrations of crystalline penicillin on the prothrombin time, coagulation time, thrombin, prothrombin consumption, labile factor, clot retraction, and protamine titration of normal blood. It was shown for the first time that penicillin did not affect prothrombin consumption, labile factor, thrombin, and protamine titration. In addition, studies that had failed to show an effect of penicillin on the coagulation time, prothrombin time, and clot retraction of normal blood were confirmed.

It seems likely that effects on blood coagulation that have been attributed to penicillin were due to impurities present in early preparations of this drug. Thus, it is concluded that when crystalline penicillin is used the possibility of an effect on blood coagulation need not be considered.

BERNSTEIN

Toohey, M.: Antagonism of Anticoagulants Dicoumarol, Tromexan, and Phenylindanedione by Vitamin K_1. Brit. M. J. **2:** 687 (Sept. 27), 1952.

An oral dose of 500 mg. of vitamin K_1 restored the prothrombin time to safe levels within eight hours. With Dicumarol (and to a lesser extent phenylindanedione) repeated doses are necessary to prevent the "rebound phenomenon" resulting from persistence of the anticoagulant drug in the body.

MCKUSICK

Losner, S. and Volk, B. W.: The Effect of Suboptimal Concentrations of Sodium Citrate upon the Clotting Times of Human and Dog Blood after Intravenous Administration of Heparin. Am. J. M. Sc. **224:** 673 (Dec.), 1952.

Suboptimal concentration of an anticoagulant solution such as sodium citrate produces a delay in the clotting time of blood. Following the administration of heparin intravenously in 25, 50, and 75 mg. doses to humans, the addition of suboptimal amounts of sodium citrate yielded markedly delayed clotting times varying with the heparin dose employed. Similar results were observed in dogs following heparin administration. The patients receiving Dicumarol manifested normal Lee-White clotting times in the tubes containing smaller amounts of sodium citrate. At higher concentrations of the latter agent, the clotting times after Dicumarol and heparin became comparable. The authors conclude that the delayed clotting time produced by the addition of suboptimal concentrations of sodium citrate to venous blood is a sensitive indicator of hypocoagulability resulting from heparin or Dicumarol therapy.

SHUMAN

CONGENITAL ANOMALIES

Dexter, L.: Congenital Defects of the Heart in High Altitudes. New England J. Med. **247:** 851 (Nov. 27), 1952.

Information from Dr. Rudolfo Limón is reported stating that in Mexico City (altitude 7,500 feet) the tetralogy of Fallot is rare but patent ductus arteriosus is common. Furthermore, severe pulmonary vascular disease is a common occurrence in association with patent ductus arteriosus, even in the early age group. Information from Dr. Victor Alzamora is reported stating that in Lima, Peru (altitude 500 feet) the incidence of patent ductus arteriosus is low, only 0.8 per 100,000 in his hospital experience, whereas the incidence is as high as 3 per 100,000 in communities in Peru at an altitude of 10,000 feet or more.

ROSENBAUM

Stachelberg, B., Lind, J., and Wegelius, C.: Absence of the Inferior Vena Cava Diagnosed by Angiocardiography. Cardiologia **21:** 583 (Fasc. 4/5), 1952.

Two cases are reported with demonstration of absence of the inferior vena cava following injection of contrast material into a malleolar vien. Venous return from the lower part of the body was effected by a large vessel passing behind the heart and emptying into the right auricle from above. The first case, a 3 month old infant, showed no evidence of other malformations while in the other, a 1 year old girl, the anomaly was associated with another venous malformation, namely a persistent left superior vena cava draining into the left auricle. The latter anomaly and an auricular septal defect were demonstrated by a second angiocardiographic study performed via the left cubital vein.

The author discusses the embryologic aspects of this type of congenital venous anomaly. The anomalous venous channel seen at angiocardiography is interpreted as a persistent right posterior cardinal vein having the combined functions of the inferior vena cava and azygos vein.

PICK

Broden, B., Jonssen, G., and Karnell, J.: Thoracic Aortography in a Case of Coarctation of the Aorta with Origin of the Right Subclavian Artery below

the Stenosis. Cardiologia **21:** 589 (Fasc. 4/5), 1952.

A 24 year old man with no history of rheumatic fever revealed a loud systolic diastolic murmur over the entire precordium with a maximum in the second and third right intercostal space. The blood pressure in the right arm was 110/80, in the left arm 170/50, and in the legs 110/100. Fluoroscopy showed enlargement of the left ventricle, left subclavian artery, and of the descending aorta and a posterior impression of the upper portion of the esophagus. On the basis of these clinical findings the diagnosis was made of coarctation of the aorta with aortic regurgitation and origin of the right subclavian artery below the region of aortic constriction. This diagnosis was fully confirmed by retrograde aortography, which revealed the region of coarctation as well as late filling of the right subclavian artery simultaneously with a well-developed collateral circulation.

PICK

Uhl, H. S. M.: A Previously Undescribed Congenital Malformation of the Heart: Almost Total Absence of the Myocardium of the Right Ventricle. Bull. Johns Hopkins Hosp. **91:** 197, 1952.

The writer describes a white female infant who died at 8 months in intractable heart failure. Autopsy revealed complete absence of the myocardium of the right ventricle except in the region of the tricuspid ring and pulmonary conus. It seemed most likely a congenital anomaly resulting from a defective or injured right cardiogenic fold.

MCKUSICK

Glenn, F., and O'Sullivan, W. D.: Coarctation of the Aorta. Ann. Surg. **136:** 770 (Nov.), 1952.

The authors attempted to evaluate the results in 18 cases of coarctation of the aorta subjected to operation. It was their opinion that a functional failure after successful anatomic correction indicated that the operation was too long delayed and that irreversible changes had taken place. They therefore concluded that the procedure should be performed early in life, despite the possibility that future growth might result in a relative stenosis.

ABRAMSON

CONGESTIVE HEART FAILURE

Mellinkoff, S. M., and Tumulty, P. A.: Hepatic Hypoglycemia; Its Occurrence in Congestive Heart Failure. New England J. Med. **247:** 745 (Nov. 13), 1952.

The clinical features of 20 cases of hepatic hypoglycemia observed at the Johns Hopkins Hospital are reviewed briefly. Of the 20 cases, autopsies were performed in 13, and in all of these there was evidence of diffuse hepatic damage upon histologic examinations. There was clinical or laboratory evidence of liver disease in all of the patients, although liver impairment had not been considered a significant feature of the illness in some of them. It is emphasized that a hypoglycemic episode may occur in a complicated clinical setting in which other manifestations of disease, such as congestive failure, are so pronounced that the symptoms of hypoglycemia are overshadowed.

There were five patients in whom hypoglycemia occurred during the course of congestive heart failure. Chronic passive congestion of the liver was considered the underlying etiology in all of them, although anorexia and improper food intake may have contributed in part. When palpitation, sweating, unusual behavior, altered consciousness or coma are present, it is important to exclude hypoglycemia as a possible cause. Determination of the blood sugar, followed by intravenous administration of small volumes of concentrated glucose if the blood sugar level is low, is recommended. It is mentioned that ready response to glucose may not occur if hypoglycemia has been present a long time, and, in fact, this condition may result in irreversible cerebral damage.

ROSENBAUM

McMichael, J.: Dynamics of Heart Failure. Oliver-Sharpey Lecture II. Brit. M. J. **2:** 578 (Sept. 13), 1952.

Severe mitral regurgitation as an isolated abnormality with massive dilation of the left auricle may cause little physical incapacitation or elevation of resting pulmonary artery pressure over a period of many years. With exercise, patients with mitral stenosis frequently show a marked increase in an already elevated pulmonary artery pressure with little change in the cardiac output. This and several bits of ancillary evidence suggest a vasoconstrictive reaction in the pulmonary arterioles. The development of pronounced elevation of resting pulmonary artery pressure in patients with mitral stenosis is frequently accompanied by extraordinarily good exercise tolerance. Digoxin occasionally increases pulmonary artery pressure without change in cardiac output, suggesting a direct effect on pulmonary vascular resistance and a result analogous to the increased systemic arterial pressure which may occur with digoxin. Apart from slowing of the ventricular rate in fibrillation, there is little physiologic evidence that digitalis is beneficial in cases of mitral stenosis. The development of pronounced tricuspid insufficiency is occasionally associated with clinical improvement of the patient. The blood regurgitating during ventricular systole is held up by the more central venous values. As a result one has the phenomenon of a higher mean pressure in the great veins near the heart than in the peripheral veins.

In pericardial effusion the rise in venous pressure may so effectively balance the external pressure on the heart that no fall in cardiac output occurs.

Although this pattern may occur occasionally in other situations, the early diastolic dip and plateau is characteristic of constrictive pericarditis.

In the cases of heart failure with acute nephritis studied by the writer, the cardiac output was normal and both it and venous pressure were not influenced by digitalis administration.

The writer indicates two types of congestive heart failure which may occur alone or may be successive stages in the same patient. In *compensatory congestion* the work of the heart is maintained by high filling pressure. Digitalis seems to have little effect. In *hypodynamic congestion* digitalis is helpful.

Acute left ventricular failure occurring with recumbency may be related to hypertension, which in turn results from peripheral vasoconstriction.

In the face of contradicting evidence the author has long since abandoned his views on the primary venous pressure reducing action of digitalis.

McKusick

CORONARY ARTERY DISEASE

Russek, H. I., and Zohman, B. L.: Progress in the "Uncomplicated" First Attack of Acute Myocardial Infarction. Am. J. M. Sc. **224:** 496 (Nov.), 1952.

The records of 1047 patients with acute myocardial infarctions confirmed by electrocardiogram were studied in an effort to evaluate prognosis. From this group 489 patients were found to have uncomplicated initial attacks in which none of the usual serious prognostic signs or symptoms were found. In this group, the mortality rate during their hospitalization was only 3.1 per cent. About half of this group died within the first 48 hours of hospitalization. Of the patients surviving more than 48 hours, the mortality rate from cardiovascular causes was 1.2 per cent. Anticoagulent therapy is not advised for this type of case because of the extremely low mortality. The authors advise that if hospitalization is deemed necessary, it should be delayed for 48 hours in order to minimize the risk entailed in transportation. The excellent prognosis for this type of patient with an acute infarction is not affected by the age of the patient.

Shuman

Anderson, M. W., Christensen, N. A., and Edwards, J. E.: Hemopericardium Complicating Myocardial Infarction in the Absence of Cardiac Rupture. Arch. Int. Med. **90:** 634 (Nov.), 1952.

Three patients who had acute myocardial infarction complicated by hemopericardium but without rupture of the myocardium or of a coronary artery are described. In two patients this complication contributed to a fatal outcome. The third patient, although critically ill, survived the episode of acute myocardial infarction and hemopericardium. Only one patient had received anticoagulant therapy.

Organizing fibrinous pericarditis secondary to acute transmural myocardial infarction was demonstrated as the source of the hemorrhage into the pericardial sac in the two cases in which necropsy was done. In one of these cases the hemorrhagic process arose in the organizing pericarditis overlying the infarct, and in the other case bleeding arose from pericarditis in areas removed from the infarcted myocardium. Hemopericardium, when suspected, requires prompt institution of anticoagulant-neutralizing measures if anticoagulant therapy has been used. Pericardial paracentesis may be a lifesaving measure when cardiac tamponade from hemopericardium occurs in the absence of a cardiac rupture.

Bernstein

Ernstene, A. C.: Complications and Sequelae of Acute Myocardial Infarction. J.A.M.A. **150:** 1069 (Nov. 15), 1952.

The prognosis of the immediate illness in acute myocardial infarction is determined principally by the size of the infarction area and by whether certain complications develop. In patients who recover, the degree of functional rehabilitation attained depends to a large extent on whether certain sequelae occur. The most important complications, that is, shock, acute left ventricular failure, congestive heart failure, disturbance of cardiac rhythm, thromboembolism, rupture of the ventricle, perforation of the interventricular septum, and rupture of a papillary muscle are discussed. The clinical features of the most common sequelae—angina pectoris, periarthritis of the shoulder, with or without the shoulder-hand syndrome, deposition of calcium in the area of infarction, aneurysm of the ventricle, permanent reduction in myocardial reserve, and cardiac neurosis—are reviewed. Where prophylactic or therapeutic measures are available these are discussed.

Kitchell

ELECTROCARDIOGRAPHY

Papp, C., and Smith, K. S.: Electrocardiographic Assessment of Posterior Cardiac Infarction. Am. Heart J. **44:** 696 (Nov.), 1952.

One hundred patients with posterior wall myocardial infarction were assessed according to the severity of the attack based on electrocardiographic findings. Twenty-two per cent were slight, 21 per cent moderate and 57 per cent severe. In slight posterior wall infarction, the following electrocardiographic patterns were shown: absent pathologic Q wave in more than one-half the cases; R-T and T changes of the subacute type, for example, bowed R-T with isoelectric take-off and deep inversion of T; and electrocardiographic restoration in about one-fourth of the cases. The severe cases exhibited pathologic Q waves in almost every instance, with high R-T take-off and a monophasic T wave in the great majority, and arrhythmias in one-third of the cases. In the moderate group, the incidence of these

signs was transitional, except that no arrhythmias were observed. There was no mortality in the slight and moderate group during the first two months. The mortality in the severe group of treated and untreated cases was 33 per cent.

Where diagnostic difficulties arose in the slight posterior wall infarctions, they were solved (1) by submitting the patients to effort tests, (2) use of leads III and aV_F recorded during deep held inspiration and (3) by finding serial changes in the electrocardiogram in several months. The use of bipolar leads as described by Slapak and Partilla for diagnostic purposes proved disappointing. The authors state that the importance of recognizing slight posterior cardiac infarction is that prompt anticoagulant treatment may prevent severe attacks.

In contrast to posterior wall infarction, slight attacks occur in anterior cardiac infarction in 42.2 per cent, moderate attacks in 22.6 per cent, and severe attacks in 35.2 per cent, respectively. The greater gravity of posterior infarction is explained by frequency of arrhythmias and by the tendency of some slight posterior wall infarctions to become severe, which is exceptional in slight anterior infarction.

RINZLER

Goldberg, L. I., Ezell, H. K., and Walton, R. P.: Electrocardiographic and Serum Potassium Changes in Fatal Hyperthermia. Am. Heart J. **44:** 754 (Nov.), 1952.

Fatal hyperthermia in anesthetized dogs under artificial respiration was produced by use of heating pads, radiation from infrared bulbs or by intravenous infusion of Dicumarol (30 or 50 mg. per kilogram) or dinitrophenol (10 mg. per kilogram) over a 30 minute period. Serum potassium values rose to high levels during the experiments producing electrocardiographic changes consistent with hyperpotassemia.

RINZLER

Scarborough, W. R., Mason, R. E., Davis, F. W. Jr., Singewald, M. L., Baker, B. M. Jr., and Lore, S. A.: A Ballistocardiographic and Electrocardiographic Study of 328 Patients with Coronary Artery Disease; Comparison with Results from a Similar Study of Apparently Normal Persons. Am. Heart J. **44:** 645 (Nov.), 1952.

The ballistocardiograms and electrocardiograms of 369 clinically normal subjects were compared with those of 137 cases of old myocardial infarction and 191 cases of angina pectoris. Sixty-nine per cent of patients with old myocardial infarction had abnormal electrocardiograms and 72 per cent had abnormal ballistocardiograms. Twenty-four per cent of patients with angina pectoris had abnormal electrocardiograms whereas 75 per cent had abnormal ballistocardiograms. In both cardiac groups, there was an increase of ballistic abnormality with age, ranging from 38 per cent in the fourth decade to 96 per cent in the seventh decade in patients with old myocardial infarction, and from 45 per cent in the fourth decade to 100 per cent in the eighth decade in the patients with angina pectoris.

When detailed quantitative analysis was made of the normal and borderline ballistocardiographs from normal subjects and from patients with coronary artery disease, it failed to reveal any important difference between the two clinical groups. Further, in the age groups in which the incidence of ballistic abnormality was low in the clinically normal subjects, it was also relatively low for patients with coronary artery disease; this same relationship held for the older age groups where there was a high incidence of ballistic abnormalities in both the cardiac and noncardiac cases.

Conclusions were drawn that significance be attached to abnormal ballistocardiograms from subjects under the age of 50 and from normal ballistocardiograms from those over the age of 60. The authors recommend that, for the present, caution be used in attributing clinical significance to abnormal ballistocardiograms from clinically normal persons and from patients whose symptoms and signs are not typical of coronary artery disease.

RINZLER

Puddu, V., Comberiati, L., and Collicelli, A.: Electrocardiographic Changes after Commissurotomy in Mitral Stenosis. Cardiologia **21:** 657 (Fasc. 4/5), 1952.

Twenty-four patients operated on for mitral stenosis had follow up electrocardiograms over periods of one to 8 months. Auricular fibrillation developed in four—in three, transiently in the first postoperative week, and in one, one month after surgery. A typical mitral P wave present in 20 cases disappeared in six. During the first week a number of cases showed transiently upward displacement of the S-T segment. Electrocardiographic signs of right ventricular strain noted prior to the operation in 17 patients disappeared completely in nine over a period of a few weeks to months. However, it developed in two patients who had no evidence of right ventricular preponderance before surgery. The over-all impression of the authors is that there is a good correlation between clinical improvement and regression of electrocardiographic abnormalities.

PICK

Kirchhoff, H. W., and Burmeister, W.: Investigations Concerning the A-V Interval in Electrocardiograms of Children. Ztschr. Kreislaufforsch. **14:** 812 (Nov.), 1952.

The authors report a statistical analysis of studies on the duration of the P-Q interval, and its relation to age and rate, in 1353 electrocardiograms of healthy children.

While steadily increasing with age in terms of

absolute values, the P-Q interval has a tendency to occupy an increasingly smaller portion of the cardiac cycle and becomes finally stabilized at a certain value. However, a definite retardation in the normal augmentation of the P-Q interval was found between the ages of 6 and 11 years. This is ascribed by the authors to a more marked susceptibility of A-V conduction in these age groups to neuroregulatory influences. They conclude that "application of rigid rules in the evaluation of A-V conduction times in children is in contradiction to physiologic facts."

PICK

Guyton, A. C., and Crowell, J. W.: A Stereovectorcardiograph. J. Lab. & Clin. Med. **40**: 726 (Nov.), 1952.

A stereovectorcardiograph utilizing a dual beam oscillograph has been developed for the instantaneous registration of the third dimensional vectorcardiogram. This apparatus is almost as simple as is the uniplane vectorcardiograph. Two vectorcardiograms are recorded simultaneously, so that the planes of these deviate from each other approximately 10 to 15 degrees. When the resultant vectorcardiograms are viewed stereoscopically by the two eyes, a third dimensional vectorcardiogram is observed. This third dimensional effect can be obtained by direct viewing of the oscilloscopic screen through an appropriate optical system or by viewing the recorded photograph with the naked eyes.

MINTZ

Segers, M.: Intermittent Preponderance. Arch. mal coeur **45**: 800 (Sept.), 1952.

The author presents electrocardiograms showing spontaneous transitions of simple left axis deviation to a pattern characteristic of left heart strain. The same phenomenon could be elicited by exercising the patient. The abnormal ventricular complexes developed with acceleration of the heart rate and disappeared with its slowing. This observation is considered to confirm previously published concepts of the author, who maintains the view that the electrocardiographic pattern of left heart strain represents a disturbance of intraventricular conduction and is not necessarily related to the presence of ventricular hypertrophy.

PICK

Moll, A.: The Effect of Cardiac Glycosides on the Unipolar Electrocardiogram. Arch. Kreislaufforsch. **18**: 210 (Sept.), 1952.

The effect of digitalis upon the contour of the electrocardiogram was studied in 100 persons including normals and patients with various types of heart disease. The characteristic change was a deviation of the S-T segment opposite in direction to the main QRS deflection. This was seen in the standard and unipolar limb leads as well as in esophageal leads. In the precordial leads the same alteration was restricted to the left sided leads in left ventricular damage, and to the right side in right ventricular pathology. In cases with chronic cor pulmonale however, the changes were atypical and pre-existent inverted T waves had a tendency to become upright following digitalization. Otherwise, alterations of the T wave (inversion) were not typical findings but occurred in cases with pathologic hearts. In some instances, especially in the presence of hyperthyroidism, extreme deviation of the S-T segment developed following usual therapeutic amounts of digitalis and was associated with clinical signs of intolerance. Such cases may represent hypersensitivity to digitalis.

In general the electrocardiogram is of no value in the evaluation of the therapeutic effects of a glycoside. However, the distribution of typical alterations in multiple precordial leads may provide supporting evidence for the type and localization of the cardiac lesion and may be helpful in the differential diagnosis of right and left heart failure. In the majority of cases the type of electrocardiographic alterations indicates that digitalis exerts its main effect upon the subendocardial layer of the myocardium. There is, however, no proof that the typical digitalis contour of the electrocardiogram indicates "myocardial damage" subsequent to the use of the drug.

PICK

Swingle, W. W., Barlow, G., Collins, E., Fedor, E. J., Welch, W. J., and Rampona, J. M.: Serum Potassium and Electrocardiographic Changes in Adrenalectomized Dogs Maintained on Cortisone Acetate. Endocrinology **51**: 353 (Nov.), 1952.

A group of seven adrenalectomized dogs was maintained for long periods of time on a low sodium diet plus a daily intramuscular cortisone dosage of 0.93 mg. per kilogram of body weight. Although the animals remained active, vigorous and free from insufficiency symptoms, the serum electrolyte pattern showed the changes characteristic of adrenal insufficiency with a decline in serum sodium and chloride and a marked elevation of the serum potassium level. Such animals were subject to sudden collapse, presumably due to the cardiac effects of the high serum potassium. Electrocardiographic studies during periods of hyperpotassemia revealed characteristic changes, such as ST segment depression, increase in T-wave amplitude with a decrease in T-wave duration, broadening and flattening of the P waves, and in some cases auricular fibrillation. Increase in the daily cortisone dosage to 1.86 mg. per kilogram, and in a few cases to 3.72 mg. per kilogram, was sufficient to restore the electrolyte pattern and the electrocardiogram to normal without any supplementary therapy.

CORTELL

Dussaillant, G., Lessandi, H., and Lepe, A.: Clinical Applications of the Electrokymographic Method. Acta Cardiol. **7**: 473 (Fasc. 5), 1952.

Following a discussion of the technic and the possible errors in the interpretation of electrokymograms, the authors report their experience in application of the method to 192 cases with various types of cardiac pathology. It proved particularly valuable in the differential diagnosis of mediastinal masses, pericardial disease and valvular and congenital lesions. In myocardial infarction five types of abnormal pulsations of the left ventricular border were found which were only exceptionally present in the absence of coronary disease. The electrokymogram is, therefore, of diagnostic importance in instances of myocardial infarction with atypical electrocardiograms (for example, in the presence of left bundle branch block).

In mitral insufficiency the authors observed abnormal systolic pulsations in the region of the left auricle and of the pulmonary veins. This, however, is diagnostic of the lesion only if recorded at various levels and on different occasions. In mitral stenosis with sinus rhythm, the left auricular wave is usually larger than normal. In insufficiency of the aortic or pulmonary valves a typical "quick" pulse contour was found over the respective ventricle. In tricuspid lesions, abnormal pulsations were observed, especially in the region of the inferior vena cava above the diaphragm comparable to alterations recorded over the left auricle and pulmonary veins in the case of mitral stenosis or insufficiency. In auricular septal defects pulsations recorded over the right ventricle were similar to those seen in pulmonary insufficiency, while in cases of patent ductus left ventricular curves resembled those of aortic insufficiency. The latter became normal after ligation of the ductus.

PICK

Van den Heuvel-Heymans, R.: Pressure Curves of the Left Atrium Recorded via Esophagus and Directly. Acta Cardiol. **7**: 537 (Fasc. 5), 1952.

A method is described of recording auricular pressure curves with the help of a balloon introduced into the esophagus to the level of the left auricle and filled with water. Representative curves under normal and abnormal conditions are illustrated along with comparable curves obtained directly during mitral surgery.

The normal esophageal pressure curve consists of a series of positive and negative waves corresponding to the different phases of auricular and ventricular contraction. The wave representing auricular contraction disappears with the onset of auricular fibrillation. Pure mitral stenosis is characterized by augmentation of the presystolic auricular wave and a protosystolic wave, which indicates bulging of the closed mitral valve into the auricular cavity. Contrary to it, the presystolic and protosystolic waves are absent in mitral regurgitation, and a large abnormal systolic wave appears due to reflux of blood into the auricle during ventricular systole. Both types of curves may occur in association, and thus the relative dynamic importance of either condition, stenosis or insufficiency, can be estimated by this method with regard to indication of mitral surgery.

PICK

Rothschuh, K. E.: Electrical Phenomena Associated with Acute Distension of a Ventricle. Ztschr. Kreislaufforsch. **14**: 801 (Nov.), 1952.

The author studied the effect of acute variations of ventricular filling upon the electrocardiogram of the frog and of the rabbit.

Progressive distension by air of a portion of the excised and perfused frog ventricle produces a decrease of monophasic potentials obtained from the surface of the distended part. The latter becomes more electronegative relative to the nondistended portion.

In the exposed heart of the rabbit, decrease of filling and output, produced by ligation of the inferior vena cava, was followed by augmentation of monophasic and diphasic deflections recorded on the heart's surface. However, with a bipolar arrangement of leads, the ST-T segment remained unaltered. Thus, a true injury effect due to impairment of filling appeared unlikely, and the increase of potentials is ascribed by the authors to a lesser degree of short-circuiting of currents, because of the diminished amount of blood present in the cavities.

Injury effects in form of marked S-T deviations, in association with reversible decrease of the size of QRS deflections, were observed in the rabbit with acute right heart dilatation due to temporary clamping of the pulmonary artery. The possible bearing of these experimental observations on electrocardiographic alterations in man, in the presence of acute and chronic cor pulmonale, are pointed out.

PICK

Uhlenbruck, P., and Schmitz, W.: The Clinical Evaluation of the Ventricular Gradient. Cardiologia **21**: 428 (Fasc. 4/5), 1952.

The authors demonstrate on several examples of clinical electrocardiograms the limitations in the practical application of calculations of the ventricular gradient. The magnitude and the angle of $\hat{G}$ can vary in different ventricular complexes of the same tracing or in the same individual on different occasions, with the phases of respiration, following excretion of edema or tapping of ascites. It is concluded that the ventricular gradient is influenced by the same or by analogous extracardiac factors which have to be considered in the clinical evaluation of electrocardiograms with low voltage. These factors may produce variations in magnitude and

inclination of the ventricular gradient similar to those seen with cardiac pathology.

PICK

Rodriguez, M. I., and Sodi-Pallares, D.: The Mechanism of Complete and Incomplete Bundle Branch Block. Am. Heart J. **44:** 715 (Nov.), 1952.

The authors report studies on the interventricular septum of dogs explored directly by an open chest method using unipolar leads and both proximal and distant bipolar leads of the electrocardiogram at different septal levels under controlled conditions as well as with varying degrees of bundle branch block. They show that septal activation is carried out from left to right at whatever level selected and that the lower levels of the septum are activated earlier than the upper regions. They point out that in the right as well as in left bundle branch block there is a delay of approximately 0.03 to 0.04 seconds which occurs in a relatively small portion of the septum (1.5 to 2 mm.) very near the right septal surface. This delay occurs precisely when the impulse passes from regions activated by the normally functioning branch to regions which were previously activated by the blocked branch. They contend that the delay represents a latency in the propagation of the impulse in this zone and suggest that no communication exists between both branches. They point out that this is the first experimental evidence of the site where the delay takes place in bundle branch block.

The process and velocity of activation of the left ventricle is the same regardless of the degree of right bundle branch block. On the other hand, minor degrees of left bundle branch block cause a delay in the time of arrival of the wave of activation to all the left ventricular septal mass but fail to modify the sense or velocity of propagation within the same mass. The sense of the activation is inverted in the whole left septal mass when the degree of block is of great magnitude, and the process is therefore carried out from right to left.

RINZLER

Duchosal, P., Veyrat, R., and Wyss, O. A. M.: Global and Focal Components of the Electrogram recorded in Unipolar Leads from the Surface of the Isolated Heart. Compt. rend. Soc. Suisse physiol. et pharmacol. in Helv. physiol. et pharmacol. acta **10:** C 50 (Dec.), 1952.

The QRS complex of unipolar leads from the surface of the ventricle of animal hearts consists of two main portions, a large positive deflection reflecting the intrinsic potential of the myocardium beneath the electrode and a smaller negative deflection of variable size and location owing to extrinsic potentials originating in the rest of the myocardium. The former is termed by the author focal and the latter global deflection.

In order to determine the relative part of these two components in the formation of a unipolar electrocardiogram, the authors compared their position within the QRS complex in a set of unipolar direct leads arranged in a semicircle along the lateral border of the right ventricle of perfused hearts of cats and rabbits. The correlation revealed that the peak of the dominant "focal" deflection occurred in the various leads at different time intervals after the onset of the QRS complex, whereas the "global" deflection, though varying in site and shape, could be found invariably in the same instant of the cardiac cycle. This demonstrates that the electrocardiographic pattern of a unipolar lead is determined by both intrinsic potentials because of the passage of the impulse beneath the electrode and extrinsic potentials coming from regions which are removed from the exploring electrode.

PICK

Fojo, P., Aixala, R., and Rabina, P.: The Study and Clinical Application of Left Dorsal Leads. Rev. cubana cardiol. **12:** 123, 1951.

Left dorsal leads are useful for recording potentials from the posterior aspect of the heart. If the electrical position of the heart is vertical, the left dorsal leads resemble aV_F; if it is intermediary, they resemble aV_L. If the heart is horizontal, the dorsal leads will be different from the unipolar limb leads.

LUISADA

Soulié, P., Joly, F., Di Matteo, J., and Folli, G.: Postoperative Modifications of the Electrocardiogram in Mitral Stenosis. Cardiologia **21:** 665 (Fasc. 4/5), 1952.

Electrocardiograms in 34 cases with mitral stenosis, three of which had auricular fibrillation, were studied for alterations developing during a follow up period of 2 to 17 months after commissurotomy. Most frequently (18 out of 22 cases) disappearance of right ventricular strain was noted. The P waves became normal in two-fifths of the cases and this more often in the precordial leads. In 10 cases the remaining changes were minor and in 12 cases the electrocardiogram became completely normal after surgery. A comparison with postoperative catheterization data revealed that improvement of the hemodynamics is more frequently associated with normalization of the ventricular complexes than with that of the P waves. However, some abnormalities of the electrocardiogram usually persist despite marked amelioration of the patient's condition.

The authors conclude that the electrocardiogram, although providing only incomplete information, remains the best method for postoperative studies in mitral stenosis.

PICK

HYPERTENSION

Pickering, G. W., Wright, A. D., and Heptinstall, R. H.: The Reversibility of Malignant Hypertension. Lancet **2:** 852 (Nov. 15), 1952.

Pickering has presented evidence in the past that the factor responsible for malignant hypertension, as opposed to benign, is long-sustained elevation of blood pressure, especially diastolic, whatever the basic cause of the hypertension may be. This sustained hypertension results in the arteriolonecrotic lesions. Cerebrospinal fluid pressure, which appears to be related in part to diastolic blood pressure, is elevated to papilledema-producing levels when hypertension is severe and sustained. This communication intends to present further evidence for his thesis, namely description of three instances of malignant hypertension manifested by papilledema and necrotic vascular lesions of the kidney in which the hypertension was converted to the benign variety by unilateral nephrectomy in one, by subtotal in another, and subtotal adrenalectomy in a third. All three patients were believed to have pyelonephritis. Postoperative followup was of six, six, and five years duration, respectively.

McKusick

Mills, L. C., and Moyer, J. H.: Treatment of Hypertension with Orally and Parenterally Administered Purified Extracts of Veratrum Viride. Arch. Int. Med. **90:** 587 (Nov.), 1952.

Of 31 ambulatory patients given "anatensol" (an extract of Veratrum viride) in an average daily dose of 7.1 mg. per day, 26 per cent had a fall in blood pressure greater than 20/10, and in one patient normotensive levels were obtained. Its therapeutic index was very low. Of 30 patients treated with an average daily dose of alkavervir (Veriloid) of 18 mg. per day, 50 per cent had a hypotensive response greater than 20/10, but only in 1 of the 30 patients could the blood pressure be reduced to normotensive levels. Its therapeutic index was also low. There was a fall in blood pressure greater than 20/10 in all 39 patients given alkavervir intravenously by continuous infusion. In 17 patients this effect was maintained for an average of 55 hours.

The therapeutic indications for Veratrum therapy are discussed, and the results obtained are compared with those of other investigators using Veratrum preparations. In addition, the effectiveness and toxicity of Veratrum preparations are compared with those of some of the newer ganglionic and adrenergic blocking agents. Hexamethonium appears to be the best single drug in the long-term oral treatment of hypertension and alkavervir administered intravenously the most satisfactory drug for short-term reduction of blood pressure in hypertensive crises.

Bernstein

Ramos, J., and Mascarcuhas, A.: The Electrocardiogram in Hypertension before and after Sympathectomy. Cardiologia **21:** 452 (Fasc. 4/5), 1952.

In 18 patients with arterial hypertension careful measurements of the electrocardiogram revealed some abnormality in the majority of instances. The earliest change was an augmentation and deviation of the ventricular gradient. This is due to increase of QRS rather than to a primary T-wave alteration. The determination of $\hat{A}QRS$ proved of greater value than a simple morphologic evaluation of the electrocardiogram. In certain patients considerable variations of abnormal T waves were noted.

Primary T-wave changes observed prior to sympathectomy disappear or become less marked following operation. In addition there occur other changes, like regression of the magnitude of $\hat{A}QRS$ and secondary T-wave changes, which can be attributed to alterations of the anatomic position of the heart or to its functional improvement, or which are due to other unknown factors. The QRS alterations occurring in hypertension cannot be correlated with the clinical course of the disease. They seem to develop on the basis of functional rather than anatomic alterations and have in sympathectomized patients no prognostic significance.

Pick

Moeller, J.: Humoral Factors in the Pathogenesis of Hypertension in Man. Arch. Kreislaufforsch. **18:** 249 (Sept.), 1952.

In normal persons intravenous injection of 12 to 20 cc. of human renin is followed by a transitory rise in blood pressure and a reduction of cardiac output while injection of only 2 cc. of the substance remains without effect. In 10 cases of acute glomerulonephritis the latter small dose produced severe reactions characterized by initial pressure elevation, bradycardia and oliguria, followed by improvement of the clinical condition. This would suggest that hypertension in acute glomerulonephritis may represent a hyperergic reaction to renin originating in the diseased kidneys. An antigenic action of renin can also be demonstrated experimentally in that the development of a Masugi nephritis can be prevented by absorption of the nephrotoxic agent with homologous renin. Such observations may represent the basis of a new therapeutic approach to acute glomerulonephritis. In chronic renal hypertension a similar hyperergic reaction to small doses of renin may occur whereas it was not observed in essential types of hypertension. Thus, the response to renin injection can be used to differentiate the two conditions.

The blood level of hypertensinogen in man can be determined by incubation of 2 cc. plasma with renin in excess, and testing the amount of newly formed hypertensin in the anesthetized cat. Since hypertensinogen is an alpha-globulin, its blood level in acute and chronic glomerulonephritis can be depressed by

restriction of proteins in the diet. In nephrotic syndromes the level of hypertensinogen in the blood was found to be low, which may account for the absence of blood pressure elevation despite severe renal involvement. The low hypertensinogen level in this condition in association with the failure to produce antibodies (evidenced by a negative renin test and susceptibility to infections) suggests insufficient function of the reticulo-endothelial system. Furthermore, the clinical pattern of nephrosis can be converted to that of glomerulonephritis (elevation of blood pressure, decrease of albuminuria and normalization of the spectrum of blood proteins) by blood transfusions. Thus it would appear, that an anergic, nephrotic phase of renal disease can be changed to a hyperergic nephritic phase by stimulation of the reticulo-endethelial system with increased production of antibodies.

PICK

Wilkins, Robert W.: New Drug Therapies in Arterial Hypertension. Ann. Int. Med. **37:** 1144 (Dec.), 1952.

In the drug therapy of the patient with essential hypertension, chief reliance has been placed upon various combinations of hydrazinophthalazine, dried extracts of Rauwolfia serpentinia, and Veratrum compounds, principally because these drugs appear to be the safest, both when used alone or in combination, of any medicinal regimen we have tried. If instituted gradually they may be given safely in ambulatory patients, with only weekly or even monthly checks of blood pressure. As a matter of fact, because they can be used together in relatively small doses, these drugs in combination may produce a greater hypotensive action with fewer symptoms or side effects than can be produced by any one of them alone. They are all effective orally, they may be given in a four-dose schedule, and they all appear to be active and well tolerated certainly for many months. Three case histories are included in order to illustrate these points.

WENDKOS

PATHOLOGIC PHYSIOLOGY

Van Den Heuvel-Heymans, G. M.: Left Auricular Pressure Curves Recorded Directly and Indirectly through the Esophagus. Acta cardiol. **7:** 537, 1952.

The pulsations of the left auricle were recorded in man through the esophagus by means of an elastic balloon connected to an electric manometer. The tracings closely resemble the pressure curves taken directly from the left auricle by means of a manometer. Typical changes were observed in patients with rheumatic lesions of the mitral valve.

The procedure is simple and of high diagnostic value. Therefore, the author recommends its extensive use whenever evaluation of the left auricular pressure is necessary.

LUISADA

Weissel, W.: Contribution to the Pathophysiology of the Pulmonary Circulation. Cardiologia **21:** 411 (Fasc. 4/5), 1952.

In 12 cases with auricular septal defects, partly associated with other types of congenital malformations of the heart, a cardiac catheter was passed into the left auricle and a pulmonary vein and pulmonary postcapillary pressures were recorded following occlusion of the pulmonary vein by the catheter tip. In no case did the postcapillary pressure exceed 33 mm. Hg, although pronounced pulmonary arterial hypertension was present in all. The presence of a considerable pressure gradient across the pulmonary capillary bed emphasizes the pathophysiologic function of the arterioles in the lesser circulation.

The postcapillary pressure curve has an arterial contour. By its correlation with the pressure curve in the pulmonary artery the delay of the pulse wave in the pulmonary circulation can be estimated. The pulse velocity appears to increase in the presence of pulmonary arterial hypertension.

PICK

Von Ahn, B.: Paroxysmal Auricular Fibrillation in Acute Nicotine Poisoning. Cardiologia **21:** 765 (Fasc. 4/5), 1952.

A 42 year old man consumed, in attempting suicide, 2 Gm. of nicotine in aqueous solution. At admission to the hospital half an hour later the pulse was slow and regular but became rapid and irregular following lavage of the stomach. The electrocardiogram showed auricular fibrillation and flat T waves in all leads. The blood pressure was 100/60. Five hours later, after violent vomiting, the pulse became regular. The next day the patient was free of symptoms, the electrocardiogram normal and clinical examination revealed no sign of organic heart disease. The possible factors causing auricular fibrillation are discussed and the opinion is maintained that the disturbance of rhythm in this case was induced by the potent dose of nicotine.

PICK

Katz, L. N., and Stamler, J.: Venous Pressure, Renal Function and Edema Formation. Cardiologia **21:** 307 (Fasc. 4/5), 1952.

The authors report results of experiments on unanesthetized dogs in which alterations of venous pressure, renal dynamics and renal electrolyte exchange were studied following ligation of large abdominal or peripheral veins.

Formation of edema was associated with sustained impairment of renal ability to excrete a hypertonic saline load. This response is apparently mediated via the renal tubules and occurs without depression of resting plasma flow, glomerular filtration rate or cardiac output, nor does it require elevation of renal venous pressure.

This mechanism also seems responsible for edema formation in chronic congestive heart failure. The

llowing complex causal relationship is assumed to me into action: Elevation of venous pressure proces reduction of circulating blood volume. The disrbance in the plasma equilibrium activates a reptor-effector system to which the kidney responds ith retention of sodium and water. This, in turn, revents a major decrement of blood volume, xtracellular fluid increases, and a new equilibrium established between osmotic and hydrostatic forces.

PICK

lount, S. G., Jr., McCord, M. C., and Anderson, L. L.: The Alveolar-Arterial Oxygen Pressure Gradient in Mitral Stenosis. J. Clin. Investigation **31**: 840 (Sept.), 1952.

Catheterization studies in patients with mitral stenosis revealed a significant reduction in the arterial blood oxygen tension as compared with the normal group, whereas the alveolar oxygen tension revealed no significant difference between the two groups. The resulting alveolar-arterial oxygen pressure gradient was significantly greater in the mitral stenosis group because of the lower arterial blood oxygen tension. This finding may be explained on the basis of increased venous admixture.

WAIFE

Burdette, W. J.: The Krebs Cycle in Human Cardiac Muscle. Am. Heart J. **44**: 823 (Dec.), 1952.

Biopsies of the human myocardium obtained by removing the auricular appendage were used by the authors to study the intermediary metabolism of this muscle and to find out whether or not the Krebs cycle is operative in the aerobic metabolism of human myocardium. Addition of pyruvate, β-hydroxybutyrate, acetate, citrate, α-ketoglutarate, succinate, malate, and pyruvate plus fumarate to slices of human cardiac muscle resulted in increased oxygen consumption of the slices. Citric acid content was greater when slices of muscle were incubated anaerobically than when they were incubated aerobically with oxalacetate. The addition of sodium arsenite to slices of human muscle in the presence of citrate resulted in the accumulation of α-ketoglutaric acid. The oxygen consumption of the tissue under these circumstances was not reduced. When malonate was added to human cardiac tissue incubated with pyruvate, citrate, malate, and pyruvate plus 0.0025M fumarate, increased respiration previously noted was inhibited. Addition of malonate to samples of muscle in a medium containing pyruvate and fumarate caused an increase in the amount of succinic acid present. The results of this study indicate that the Krebs cycle is operative in the intermediary metabolism of human cardiac muscle.

RINZLER

tajano, C., Scandroglio, J. J., and Passano, A. M.: Experimental Reflex Pulmonary Atelectasis. Sistole **3**: 1, 1952.

Rapid intravenous or intracarotid injection of 10 cc. of physiologic salt solution at three-minute intervals caused, after the third injection, interstitial edema of the lungs and foci of pulmonary atelectasis in the dog. The authors believe that similar accidents may occur in patients after rapid injections like those used in arteriography and phlebography.

LUISADA

McCord, M. C., and Blount, S. G., Jr.: The Hemodynamic Pattern in Tricuspid Valve Disease. Am. Heart J. **44**: 671 (Nov.), 1952.

The hemodynamic pattern in tricuspid valve disease was evaluated in four patients with rheumatic valvular heart disease and clinical evidence of tricuspid regurgitation by electrocardiography, roentgenography, cardiac catheterization and by clinical examination. From right auricular pressure curves, it was seen that all tracings demonstrated that the normal systolic pressure dip, the "x" dip, was replaced by a plateau or positive wave, the amplitude of which varied depending on the severity of tricuspid insufficiency. This study also suggested that the amplitude of the regurgitant wave in the auricle was the most valid basis for establishing the presence of organic tricuspid disease. Study of the right ventricular pressure curve indicated that the pressure level at the nadir of the early diastolic dip was a more accurate indication of the presence of failure of the right ventricle in patients with organic tricuspid regurgitation than is the plateau level in diastole.

RINZLER

Delorme, E. J.: Experimental Cooling of the Bloodstream. Lancet **6741**: 914 (Nov. 8), 1952.

The author studied the physiologic effect of cooling the blood stream in 33 dogs. This was accomplished by circulating the blood through a refrigerating system and then returning it to the body. By this method, body temperatures were dropped to between 22 and 26 C., and then various procedures, such as the production of shock and asphyxia, were carried out.

Uncomplicated recovery occurred in all but four dogs. No histologic damage was subsequently noted, and none of the functional changes was found to be irreversible. The effect of cooling in preventing the usual sequence of late events in shock was considered to be due not only to the reduced oxygen demand of the tissues but also to depression of harmful enzyme activity generally elicited in the presence of injury of cells by anoxia.

It was concluded that at a body temperature of 25 C. dogs can survive drastic and prolonged reductions in blood volume, as well as suspension of blood flow, both locally and systemically. The various clinical implications of such a procedure are apparent.

ABRAMSON

Gill, R. J. and Duncan, G. G.: The Clinical Use of Alginic Acid as a Cation Exchanger. Am. J. M. Sc. **224:** 569 (Nov.), 1952.

Alginic acid employed as a cation exchanger is a polymeric anhydro-B-D-mannuronic acid obtained from giant kelp. The administration of this agent to hypertensive patients failed to produce a reduction in diastolic pressure such as was obtained in the same patients previously treated with synthetic resin. The urinary sodium levels were higher during alginic acid administration than during the period of carboxylic resin therapy. Three edematous patients were treated with this new exchanger, of whom only one had a diuresis. In these patients, the synthetic resin was more effective and produced lower sodium levels. Alginic acid was well tolerated and produced no electrolyte disturbance except for a slight rise in serum potassium in one patient. The authors conclude that alginic acid is less efficient as a cation exchanger than the carboxylic resin.

SHUMAN

Tunis, M. M. and Wolff, H. G.: Analysis of Cranial Artery Pulse Wave in Patients with Vascular Headache of the Migraine Type. Am. J. M. Sc. **224:** 565 (Nov.), 1952.

Episodic head pain arising from cranial or intracranial vascular structures have several characteristic features. (1) A pulsatile quality; (2) intensity of pain is augmented by procedures increasing intravascular pressure such as head-down position or administration of pressor agents; intensity of pain is diminished by procedures which diminish intravascular pressure in the arterial system of the head; (3) during heacache, enlarged arteries may be noted with associated edema of skin at site of headache, the arterial wall is tender, and the skin is hyperalgesic; (4) intensity of headache is diminished by pressure upon the arteries or by the application of local analgesics to the involved arteries. Frequently the superficial temporal artery is the source of the headache.

The cranial artery pulse waves were studied in patients with vascular headache by means of an arterial pressure cup and an electrocardiograph type recorder; the bulbar conjunctival vessels were observed by means of slit lamp. Just prior to the onset of headache, the normal pulse wave contour was altered to one of vasoconstriction during which visual scotomata were reported by some patients. Following the onset of head pain, the pulse tracings showed a progressive increase in amplitude. A sharp, forceful pulsation was palpable associated with enlargement of the vessel in the involved area. During the course of the headache, further alterations of the pulse wave contour were noted. The changes are indicative of vascular dilatation, hyperemia and diminished resistance to blood flow. Slit-lamp examination of the conjunctival vessels demonstrated inadequacy of the minute vessel drainage and an increased resistance to blood flow from the involved arterial bed. The vessel walls are thickened with evidence of vascular and perivascular edema, the intraluminal diameters are diminished. These vascular alterations were absent on the contralateral side.

The authors concluded that vascular headache results from increased tension within or about pain sensitive cranial artery walls; dilatation and distention of the involved vessels are fundamental mechanisms in the production of pain. The associated edema of the vascular structures intensifies the effect of headache.

SHUMAN

Threefoot, H. K.: The Response of Venous Pressure of Man to a Hot and Humid Environment. Am. J. M. Sc. **224:** 643 (Dec.), 1952.

Normal male subjects were exposed to a controlled hot and humid environment after preliminary determinations of venous pressure were obtained under normal conditions. Venous pressure readings were made in the hands, feet and median basilic veins. The limits of tolerance of the subjects to the hot environment of 45 C. was 49 minutes as an average. At the end of the exposure period, the venous pressure was found to be raised in all veins tested. The increase in the upper extremities was greater than that observed in the lower extremities. Changes in the blood pressure were variable; the pulse rate increased in each subject. There was no correlation between changes in venous pressure and those in arterial pressure, pulse rate or rectal temperature.

SHUMAN

Episcopo, U.: Observations on Arrhythmias during Catheterization of the Heart in Man. Acta cardiol. **7:** 595 (Fasc. 6), 1952.

Continuous electrocardiographic recordings during cardiac catheterization of 40 patients with congenital or rheumatic heart disease are reported. In 38 cases (95 per cent) various types of arrhythmias occurred, for example, ventricular premature beats and runs of ventricular tachycardia, supraventricular tachycardia in a case with Wolff-Parkinson-White syndrome, persisting auricular fibrillation, transient complete A-V block and transient right bundle branch block. There appears to be a relationship between the location of the tip of the catheter and the type of arrhythmia induced. Particularly sensitive regions seem to be the tricuspid valve, the septum and free ventricular wall and the pulmonary artery. However, one patient developed an arrhythmia (A-V dissociation) before the catheter entered the heart.

The author concludes that cardiac catheterization should always be performed under permanent electrocardiographic control in order to recognize the

onset and nature of the arrhythmia which may develop and to institute proper measurements without delay.

PICK

PATHOLOGY

Kisch, B.: Electron Microscopy as Applied to Cardiology. J. Mt. Sinai Hosp. **19:** 606 (Nov.–Dec.), 1952.

The author presents a summary of his studies of heart muscle by means of electron microscopy. Each muscle fiber of the heart has a diameter of 10 to 20 microns and contains between 300 to 700 myofibrils of a diameter of about 0.2 to 0.5 micron each. These myofibrils are independent units connected to each other only by a Z-band system which in itself is attached to the sarcolemma of each muscle fiber. The Z-band system probably serves to keep the myofibrils, or contractile part of the system, in order, but in addition has a biochemical function. The Z-band system is responsible for the visual impression of cross striation.

Nuclei are present imbedded between the myofibrils and always surrounded by endoplasm.

In adequately treated sections of the heart a very great number of small, partly submicroscopic bodies are always recognizable, which are arranged in long rows between the myofibrils and are probably what previous investigators have referred to as sarcosomes. However, electron microscopy studies have shown them to be of different types, some ovoid, some granular, and others band-shaped, resembling mitochondria. Their close association with the Z-band system makes it likely that this system plays a part in their formation. The sarcosomes may well serve as a site of enzyme concentration, needed by the cell for rapid restoration in the chemical chain of muscular contraction.

The existence of hundreds of myofibrils encased in one muscle fiber suggests that the generators of electromotive forces are probably the individual myofibrils, which at rest have the same electric charge, electrostatic forces keeping them apart and in order. Further studies of these properties will be of help in elucidating the mechanisms responsible for the electrocardiogram.

CORTELL

PHARMACOLOGY

Strauss, V., Simon, D. L., Iglauer, A., and McGuire, J.: Clinical Studies of Intramuscular Injection of Digitoxin (Digitaline Nativelle) in a New Solvent. Am. Heart J. **44:** 787 (Nov.), 1952.

The intramuscular administration of digitoxin (Digitaline Nativelle), dissolved in a combination of polyethylene glycol 300 (39 per cent), benzyl alcohol (4 per cent), ethyl alcohol (4 per cent), distilled water (19 per cent) and glycerine (44 per cent) was evaluated in 21 patients with auricular fibrillation and congestive heart failure. Digitalis preparations were withheld in these patients until the ventricular rate became rapid, with a pulse deficit, and until signs and symptoms of cardiac failure appeared. An electrocardiogram was then taken and digitalization begun by an intramuscular injection of 0.6 mg. (3 cc.) of digitoxin in each gluteus maximus, a total of 1.2 mg. In 11 patients, eight of whom had been previously treated by the intramuscular route, digitoxin was administered orally in identical dosage. Decrease of the initial ventricular rate occurred following rapid intramuscular digitalization in all patients. From an average initial ventricular rate of 100 beats per minute, the rate fell to an average of 77 beats per minute after four hours. The ventricular rate could be kept at a desired level of 65 to 85 beats per minute by the intramuscular administration of 0.2 mg. daily. Signs and symptoms of congestive heart failure were controlled in all patients. Very slight to moderate pain followed the injection of the initial digitalizing dose. The oral studies were comparable to the intramuscular studies with respect to speed of digitalis effect, final pulse rate and ease of maintenance.

RINZLER

Herrell, W. E.: Antibiotic and Chemotherapeutic Agents in Infections of the Blood Stream and Heart. J. A. M. A. **150:** 1450 (Dec. 13), 1953.

Recent developments in therapy for infections of the blood stream and heart not only have proved the value of sulfonamides and the antibiotics but also have demonstrated that their use in some cases serves to complicate the situation. Once the causative organism is isolated, the outcome of therapy in these conditions depends on several important factors: (1) early recognition and early adequate treatment, (2) exact knowledge of the sensitivity of the organism to various antibiotics or combinations of antibiotics, (3) recognition and removal of foci of infection, and (4) duration of therapy. Very often therapeutic failure occurs because the patients have not been treated sufficiently early but empiric treatment with antibiotics before blood cultures have been obtained is thoroughly condemned. Empiric therapy is justified and recommended only after one or two blood cultures have been obtained before treatment is started. Sudden development of acute vegetative endocarditis is another significant cause of therapeutic failure in the treatment of uncomplicated bacteremia. The presence of localized abscesses in the brain, liver, kidneys or lungs may also contribute to failure. Other reasons for poor results may be renal failure, acute cardiac failure, or on occasion the development of embolic phenomena or rupture of mycotic aneurysms. The article discusses the laboratory, clinical and therapeutic aspects of subacute bacterial endocarditis. The prophylaxis of rheumatic fever by the use of sulfonamides and anti-

biotics is also considered, as is the treatment of suppurative pericarditis and wounds of the heart.

KITCHELL

Wang, S. C., and Borison, H. L.: A New Concept of Organization of the Central Emetic Mechanism: Recent Studies on the Sites of Action of Apomorphine, Copper Sulfate and Cardiac Glycosides. Gastroenterology **22:** 1 (Sept.), 1952.

From experiments performed on 150 dogs it has been affirmed that apomorphine induces vomiting solely through a central action. This action is on receptors located in the chemoreceptor trigger zone. Experiments with copper sulfate performed on 154 dogs revealed that this substance can induce emesis through two different actions: (1) "reflex vomiting," due to gastrointestinal irritation and (2) "central vomiting," due to excitation of the chemoreceptor trigger zone by circulating copper. Experiments on digitalis emesis are presented to illustrate the suggested procedure. Trigger zone ablation sharply reduces the incidence of emesis following both intravenous and oral doses of Scillaren A and lanatoside C. The emetic response to digitalis is not impaired either by gastrointestinal denervation or by cardiac denervation. From these findings we conclude that digitalis has an important central (chemoreceptor trigger zone) component of action but that it also acts peripherally at a receptor site, yet unknown, which lies outside of the gastrointestinal tract.

BERNSTEIN

Hine, C. H., Shick, A. F., Margolis, L., Burbridge, T. N., and Simon, A.: Effects of Alcohol in Small Doses and Tetraethylthiuramdisulphide (Antabus) on the Cerebral Blood Flow and Cerebral Metabolism. J. Pharmacol. & Exper. Therap. **106:** 253 (Nov.), 1952.

The authors determined cerebral blood flow in 10 male patients with alcoholic histories by means of blood samples collected from the internal jugular bulb and femoral artery while the patient was breathing a gaseous mixture of nitrous oxide, oxygen, and nitrogen. Four separate tests were performed on each patient—a control, a second determination after a dose of alcohol, a third after four days of Antabus therapy and a fourth after a dose of whiskey given while the patient was under Antabus. With alcohol or Antabus alone a slight (about 15 per cent) decrease in cerebral blood flow was found with metabolic changes in line with this decrease. The authors question the significance of the decrease in cerebral blood flow because the changes might be due to the lessened apprehension of the patients in the second and third determinations because of familiarity with the test. Following the alcohol-Antabus reaction there was a significant increase in the cerebral blood flow accompanied by a depression of cerebral oxidative processes. Determination of blood acetaldehyde levels during these studies demonstrated that the brain is capable of metabolizing acetaldehyde and that Antabus interferes somewhat with acetaldehyde metabolism in vivo.

SAGALL

Basmajian, J. V.: The Distribution of Valves in the Femoral, External Iliac, and Common Iliac Veins and their Relationship to Varicose Veins. Surg. Gynec. & Obst. **95:** 537 (Nov.), 1952.

A series of 38 cadavers was studied with regard to the location of valves in the main veins of the lower extremity. These structures were found above the saphenofemoral junction in about 80 per cent of cases. Only rarely was no valve noted in the whole length of the femoral vein, while in most instances two were present in this location. The common iliac vein was not found to contain any of these structures.

It was concluded that the presence or absence of valves in the main venous trunk above or proximal to the mouth of the greater saphenous vein is, at most, only of theoretic importance in the etiology of saphenous varices.

ABRAMSON

Lans, H. S., Stein, I. F., Jr., and Meyer, K. A.: Diagnosis, Treatment and Prophylaxis of Potassium Deficiency in Surgical Patients; Analysis of 404 Cases. Surg., Gynec. & Obst. **95:** 321 (Sept.), 1952.

The authors presented a study of potassium deficiency based upon an analysis of 404 surgical patients. Of this number 241 had a serum potassium below 3.7 milliequivalents per liter preoperatively and 69, postoperatively.

Clinical symptoms of hypopotassemia consisted of muscular weakness, gradual in onset and of increasing severity, anorexia and nausea, and confusion. Shallow respirations, abdominal distension, paralytic ileus, irregular pulse, and a fall in blood pressure were common findings. The electrocardiographic signs consisted of a lengthening of the Q-T interval, a reduction in the height and a widening of the T wave, and later, inversion of this wave with a sagging of the ST segment. However, in some instances low potassium levels were associated with normal tracings.

Administration of potassium chloride intravenously was frequently followed by prompt clinical improvement. The duration of treatment required to restore the serum potassium to normal averaged three days. The solutions used contained 3 Gm. of potassium chloride in a liter of intravenous fluids, given at the rate of 8 to 12 cc. per minute.

ABRAMSON

Reader, S. R.: The Effective Thermal Conductivity of Normal and Rheumatic Tissues in Response to Cooling. Clin. Sc. **2:** 1, 1952.

The author compared the changes in temperature and effective thermal conductivity in the subcutaneous tissues and muscle of normal and rheumatic subjects, in response to cooling of the overlying skin. Needle thermocouples were inserted into the tissues through a bleb of local anesthetic. An area of the lumbar region was cooled until thermal equilibrium was attained, and then tissue temperature gradients were measured. Heat flow was estimated by gradient calorimetry, and from this figure effective thermal conductivity was calculated.

It was found that the rheumatic groups and the female control group of comparable age corresponded closely in respect to tissue temperature and effective thermal conductivity after cooling. In the control groups, the males developed lower tissue temperatures than the females. The effective thermal conductivities for the subcutaneous layers were similar in all groups, but in the muscle layer the older subjects of both sexes developed lower values.

It was concluded that the responses of the rheumatic subjects did not differ from those of a comparable control group.

ABRAMSON

Goldmann, M. A., and Luisada, A. A.: Alcohol-oxygen Vapor Therapy of Pulmonary Edema: Results in fifty attacks. Ann. Int. Med. **37:** 1221 (Dec.), 1952.

Over a period of more than 18 months, ethanol-oxygen-vapor was administered to 45 patients for 50 attacks of pulmonary edema. Forty of the attacks were paroxysmal and 10 were of a protracted nature. Two methods of administration of this mixture were used. In one method, 95 per cent alcohol replaces the water in the humidifier which is attached to an oxygen tank, and its vapors are introduced through a catheter placed in the nostril as the oxygen flows through the system. In a second method, a mask, with or without positive pressure, may be used in place of the nasal catheter with the same equipment. When this is done, 30 to 40 per cent ethanol is used in the humidifier, since higher concentrations are usually not well tolerated. A mask may also be used with standard equipment for gas anesthesia and 30 per cent ethanol placed in the ether container. Any technic involving the use of a mask is less desirable in the conscious, apprehensive patient; moreover, it impairs his ability to expectorate the fluid resulting from liquefaction of foam. On the other hand, it is the most suitable in the unconscious patient. Ethyl alcohol vapor and oxygen by inhalation were used exclusively in 14 attacks. An excellent result, frequently with dramatic improvement, was noted in 12. Ethyl alcohol-oxygen vapor was used after failure of conventional therapy in 23 attacks. Objective improvement occurred in 15. Six other attacks responded similarly, but a waning effect of previous therapy could not be altogether discounted. The benefits of this type of treatment are ascribed to the antifoaming action of the ethanol vapor which supposedly liquefies the expectorate. However, the importance of such factors as moderate peripheral vasodilatation and mild central sedation, as seen within the first half-hour of therapy in several of the patients, cannot be completely discounted. Furthermore, there may be a possible direct or indirect relaxing effect on the tracheobronchial tree, in addition to the other factors mentioned.

WENDKOS

Porto, J., and Cordeiro, R.: Pressure Alterations of the Pulmonary Circulation Produced by a Poison (Silver Nitrate). Cardiologia **21:** 421 (Fasc. 4/5), 1952.

The authors produced in dogs acute pulmonary edema by injection of silver nitrate into the right or left circulation. The experiments were performed with recording of alterations of the pressure in the cardiac cavities and big vessels. Following injection of the substance into one of the venae cavae or the right ventricle the pressure in the latter rose instantaneously but fell in the left side of the circulation. Following injection into the left ventricle or into the aorta the pressure rose simultaneously in the systemic and pulmonary circulation. At autopsy of the animals, multiple small emboli were found in the lungs or brain, according to the site of injection. These microemboli consisted of a complex colloid compound formed by reaction of the silver nitrate with the plasma proteins.

The common finding following injection of silver nitrate into the right or left circulation was the acute development of pulmonary hypertension terminating in fatal pulmonary edema. The authors believe that acute left heart failure is not the cause but a concomitant feature of pulmonary edema. To explain the onset of pulmonary hypertension following injection of silver nitrate into the systemic circulation "angio-neurogenic factors" are implied.

PICK

Hehre, F. W.: An Evaluation of Positive Pressure Transfusions. Anesthesiology **13:** 621 (Nov.), 1952.

Under certain circumstances positive pressure transfusions have definite advantages over those administered by gravity. For example, when blood loss is excessive, rapid intravenous transfusion under pressure should be utilized. Arterial transfusion is superior to venous transfusion only because it supports the blood pressure while blood volume is being replaced. This factor is important in the more profound state of shock, in which there is a reduction in coronary flow, and the heart itself, along with the liver, brain and kidneys, becomes anoxic. Intra-arterial transfusion forces oxygenated blood, ejected from the heart, back into the coronary arteries under a relatively normal diastolic pressure.

There are several dangers in the use of transfusions under positive pressure. The first is an embolus, which can be prevented through careful supervision of the procedure. Another untoward effect is gangrene of the extremity utilized in the transfusion. This may occur as a result of the initiation of spasm of the main arteries, produced by pumping in cold blood under high pressure. If such a state is produced, the ischemic changes may be minimized by the local use of procaine and regional sympathetic block. Congestive heart failure may be a complication of too rapid intravenous pumping. However, with the aid of repeated determinations of peripheral venous pressure during the procedure and the regulation of the rate of transfusion accordingly, this possibility can be eliminated. Finally, an increased bleeding tendency and tetany may result, presumably from the large amounts of citrate in stored blood binding the ionized calcium of the circulating blood.

ABRAMSON

Gilmore, H. R., Kopelman, H., McMichael, J., and Milne, I. G.: The Effect of Hexamethonium Bromide on the Cardiac Output and Pulmonary Circulation. Lancet **2:** 898 (Nov. 8), 1952.

In four patients who received C_6 (hexamethonium bromide) intravenously both systemic and pulmonary blood pressure fell without a significant change in cardiac output. Cardiac outputs in the horizontal and the semi-upright (tilted) position were compared both before and after C_6 administered subcutaneously. Tilting resulted in a decrease in cardiac output which was no greater after C_6. Studies using the Evans blue dye curve produced evidence that the author's term "cardiopulmonary blood volume" is increased after C_6 and does not show the normal reduction with tilting. Since the roentgenogram showed no increase in cardiac volume with tilting it was concluded that the drug prevented the normal reduction in lung vascular capacity which occurs in the foot-down position. A vasoconstrictor nervous mechanism regulating the pulmonary vessels and blocked by C_6 was suggested by the last finding and by the fall in pulmonary artery pressure.

MCKUSICK

Lauener, H., and Bovet, D.: The Mechanism and Pharmacodynamic Modification of Atropine Tachycardia in the Nonanesthetized Dog. Helvet. physiol. et pharmacol. acta **10:** 413 (Dec.), 1952.

The cardio-acceleratory qualities of atropine were investigated in nonanesthetized dogs. The effect of the drug was compared with that of other parasympathicolytic agents having no central stimulating action like atropine. The experiments confirmed the classic concepts of a paralyzing effect of atropine upon the vagi. Atropine also induced tachycardia in animals in which the thoracic sympathetic ganglia and the stellate ganglion were resected, provided the vagal nerves were intact. This proves the presence of cardio-accelerating fibers in the vagus nerve.

In the course of these experiments a series of widely used drugs were tested concerning their effect on tachycardia produced by atropine. Barbiturates in high narcotic doses depressed the heart rate but had no or only little effect in small sedative dosage. Ganglionic blocking agents lower the heart rate in the atropinized dog, whereas sympathicolytics, even in high doses, do not.

PICK

Burdette, W. J.: Increase in Oxygen Consumption of Human Cardiac Muscle Incubated with Lanatoside C. J. Lab. & Clin. Med. **40:** 867 (Dec.), 1952.

This report is an account of the effect of Lanatoside C on the oxygen consumption of slices of human auricular appendage, obtained by cardiac biopsy at the time of a thoracotomy.

Although the number of determinations is restricted by the limited availability of human tissue, there was clear-cut evidence that Lanatoside C caused an increase in oxygen consumption. The mechanism of this action and its relation to contraction was not clear, but it seems permissible to conclude that there was a direct effect of this cardiac glycoside on the human myocardium.

MINTZ

Talley, R. W., Beard, O. W., and Doherty, J. E.: Use of Pentaerythritol Tetranitrate (Peritrate) In Treatment of Angina Pectoris. Am. Heart J. **44:** 866 (Dec.), 1952.

The usefulness of pentaerythritol tetranitrate (Peritrate) in decreasing the severity and/or frequency of angina pectoris was evaluated in 14 patients with angina pectoris who had been under previous observation and treatment for periods ranging from three months to four years. The diagnosis of angina pectoris in each case was established by the typical history and substantiated by abnormal ballistocardiograms in 13 patients and abnormal electrocardiograms in 12 patients, and a positive Master two-step test in the remaining two patients. The control period was at least two weeks. Then Peritrate was started first in 11 patients in doses of 10 to 20 mg. three times daily while the remaining three were given a placebo at first. The average duration of administration of 30 mg. daily of Peritrate was five weeks, of 60 mg. daily was 5.3 weeks and of the placebo was 5.1 weeks. The placebo and Peritrate tablets resembled each other in all respects except that the placebo tablet was not scored. No blindfold technic is mentioned by the authors. Records of the exact time of each episode of angina and whether the attack was relieved by rest or nitroglycerin were kept by the patients who were seen at weekly or biweekly intervals. Analysis of the results

showed that Peritrate in doses of 30 or 60 mg. daily was no more effective than a placebo in reducing the number of attacks of angina.

RINZLER

Aikawa, J. K.: Comparison of the Thiocyanate and Radiosodium Spaces in Disease States. Am. J. M. Sc. **224**: 632 (Dec.), 1952.

Extracellular fluid volumes were measured by injections of radioactive sodium and sodium thiocyanate simultaneously together with the blood volume using T-1824 dye and hematocrit in four normal subjects and 25 patients with various diseases. In the control group, the radiosodium and thiocyanate spaces were identical, averaging 255 ml. per kilogram. The extracellular volume in the majority of diseased patients was greater than in the control group, but there was considerable disparity between the results with the two methods. Eighteen determinations showed the radiosodium space greater than the thiocyanate space. A radiosodium space greater than 330 ml. per kilogram was usually associated with clinical edema.

Although both methods measure a larger volume of fluid than is usually accepted as extracellular space, they provide information of physiologic significance. The magnitude of the radiosodium space may be used as an index of fluid retention associated with decreased renal function in congestive failure or nephritis. Alteration of cell membrane permeability in certain other disease states in the absence of edema is accompanied by an increase in the radiosodium space.

SHUMAN

Justice, T. T., Jr., Allen, G. W., and Cronheim, G. E.: Studies with two New Theophylline Preparations. Am. J. M. Sc. **224**: 647 (Dec.), 1952.

The oral administration of theophylline compounds was investigated in several groups of patients with hypertension and congestive heart failure. The new theophylline salts studied were theophylline sodium nitrite and theophylline sodium ascorbate. Blood levels of theophylline following their administration and following aminophylline were all comparable. The nitrite-containing compound produced a drop in blood pressure of moderate degree in a small number of hypertensives at a high dose level. Sodium nitrite alone produced similar results. The ascorbate-containing compound produced the same type of diuretic effect observed with the use of aminophylline in patients with congestive failure. There was slight temporary reduction of blood pressure in a small group of patients receiving theophylline sodium ascorbate. There were no differences in the tolerance of these various compounds at the dose levels required for therapeutic effect. Only about 40 per cent of the patients were able to tolerate the daily administration of 1 Gm. of theophylline.

SHUMAN

PHYSICAL SIGNS

Leatham, A.: Phonocardiography. Brit. Med. Bull. **8** (4): 333, 1952.

The principles of phonocardiography are reviewed. Recent studies from the author's laboratory on the "pulmonary second sound" are presented. Whereas the "aortic second sound" has its origin almost exclusively in the aortic value, the pulmonary second sound has both an aortic and a pulmonic component. Potain in 1866 first noted the splitting of the pulmonary second sound at the end of inspiration in healthy subjects. Using the delay in the pulmonic component which occurs with inspiration, the author describes the findings in simultaneous phonocardiograms from two or more sites in pulmonary hypertension, bundle branch block and pulmonic stenosis. The "opening mitral snap," split pulmonary second sound, and third heart sound can be distinguished even when all present in the same individual by the author's technic of synchronous multiple phonocardiograms. The origin—mitral or aortic—of systolic murmurs at the apex can be identified. The aortic stenosis murmur reaches a maximum in midsystole diminishing rapidly thereafter and finishing before the second sound. The murmur of mitral incompetence is pansystolic, often drowning the second sound at the apex. The systolic murmur of ventricular septal defect reaches the aortic component of the normally split pulmonary second sound but stops before the pulmonic component. Mention is not made of determination of the origin of basilar diastolic murmur by their relationship to the aortic or pulmonic components of the pulmonary second sound. The continuous murmur of patent ductus arteriosus or of aortopulmonary fistula is easily distinguished from to-and-fro aortic systolic-diastolic murmurs.

MCKUSICK

PHYSIOLOGY

Wileus, S. L. and McCluskey, R. T.: The Comparative Filtration Properties of Excised Arteries and Veins. Am. J. M. Sc. **224**: 540 (Nov.), 1952.

Iliac arteries and veins were obtained at necropsy and examined for the filtration rate of fluids escaping through the vessel wall under controlled test conditions. Both vessels were found to be freely permeable to the smaller molecular substances. They were found to be impermeable to substances such as the cholesterol of egg-yolk solution, and India ink. The excised veins had greater porosity than arteries with a more rapid transit of fluid and higher proportions of colloid escaping from them. These differences in diffusion rates may be dependent upon the differences in structure of the two vessels. The greater retention of colloids within the arterial lumen increases the colloidal osmotic pressure above that found in the veins. Filtration of serum lipid and other partially filtered substances through arterial

walls results in their being deposited at these sites according to the authors. The looser structure and greater permeability of veins permits transmigration of these substances without deposition.

SHUMAN

Croxatto, H., Barnafi, L., and Passi, J.: Effect of Renin on Diuresis in Rats. Science **116:** 507 (Nov. 7), 1952.

Early experiments showed that renin might have a diuretic effect in the experimental animal. This study investigated the conditions which effect this renin diuretic activity. In normally hydrated rats drinking tap water, the intraperitoneal administration of renin considerably increased urinary excretion, although the same dose subcutaneously had slight if any activity. The diuretic action decreased on repeated injections; this behavior may be explained by the formation of antirenin. Inactive kidney extracts do not stimulate diuresis.

The diuretic action of renin is considerably increased in animals drinking 1 per cent sodium chloride. Under these circumstances subcutaneous renin is also effective. Hypertensin has a very weak diuretic effect. Adrenalectomy markedly reduced the diuretic stimulation of renin.

The first effect, an inhibition of diuresis, lasts from one-half to one hour; this is followed by a prolonged phase from the second to the fifth hour and is characterized by an elevation of water excretion.

WAIFE

Levy, R. L.: Comparison of the Effects on the Circulation of Ascending an Incline and Mounting Stairs. Cardiologia **21:** 488 (Fasc. 4/5), 1952.

In five normal persons and in five patients with coronary heart disease the effect of various types of effort upon cardiac work was investigated. The exercise employed consisted in ascending a ramp, mounting a flight of stairs, descending the stairs and walking on level ground. The ballistocardiogram was used for determination of cardiac output and pulse pressure; heart rate and calculations of stroke volumes and cardiac work were recorded.

On repetition of a given exercise the effects on the circulation showed considerable variations in the single individual as well as between individuals composing a group. However, in both normals and cardiacs, it was found that ascent of a short incline, like mounting an ordinary staircase, does not impose a marked burden of work upon the heart. The response of a patient with compensated coronary disease is not significantly greater following this exercise than after descent and is only slightly greater than after walking for an equivalent distance on the level. The authors conclude that patients with coronary disease may safely be permitted to ascend inclines of moderate steepness and length provided the ascent can be performed without undue dyspnea or anginal pain.

PICK

Baldwin, D., Robinson, P. K., Zieler, K. L., and Lilienthal, J. L., Jr.: Interrelations of Magnesium, Potassium, Phosphorus, and Creatine in the Skeletal Muscle of Man. J. Clin. Investigation **31:** 850 (Sept.), 1952.

Human skeletal muscle, obtained by biopsy, was analyzed directly for intracellular magnesium, potassium, and phosphorus. Constant intracellular proportions of these substances were observed despite wide variations in the serum.

In normal muscle the mean values of potassium, magnesium, phosphorus, and creatine were respectively 3.5 mEq., 0.61 mEq., 0.065 Gm., and 0.138 Gm., referred to 1 Gm. of noncollagenous nitrogen. In atrophied muscles the cation concentrations were reduced in terms of wet weight, but when referred to noncollagenous nitrogen, were identical with the normal series.

WAIFE

Dressler, S. H., Slonim, N. B., Balchum, O. J., Bronfin, G. J., and Ravin, A.: The Effect of Breathing 100% Oxygen on the Pulmonary Arterial Pressure in Patients with Pulmonary Tuberculosis and Mitral Stenosis. J. Clin. Investigation **31:** 807 (Sept.), 1952.

Twenty-two of 27 studies in patients with pulmonary tuberculosis revealed a decrease in pulmonary arterial pressure with oxygen. Similarly, 21 of 25 studies in patients with mitral stenosis showed a decrease in pulmonary arterial pressure with oxygen. This decrease during oxygen breathing could be due to either a reduction in the volume of blood flow through the pulmonary vascular bed, a diminution of pulmonary vascular resistance, or a fall of the left auricular and pulmonary venous pressure. This study was performed in Denver, there the arterial oxygen tension is somewhat lower than at sea level. Possibly the effect of oxygen at this altitude is to abolish a slight relative anoxemia which normally exists there.

The beneficial effect of oxygen therapy on patients with acute or chronic pulmonary hypertension may depend not only upon such factors as arterial oxygen tension, decreased cardiac output, and decreased cardiac rate, but also upon a decreased pulmonary arterial pressure, a factor which would further reduce the work of the right ventricle.

WAIFE

RHEUMATIC FEVER

Sabiston, D. C., Jr., and Follis, R. H., Jr.: Lesions in Auricular Appendages Removed at Operations for Mitral Stenosis of Presumed Rheumatic Origin. Bull. Johns Hopkins Hosp. **91:** 178 (Sept.), 1952.

The auricular appendages from 43 patients submitted to mitral commissurotomy were examined microscopically. All cases (nine) with elevated sedimentation rates had lesions characteristic of the

heumatic state. Twenty-three other cases with nor-
al sedimentation rates had lesions of lesser degree.

McKusick

Hill, A. G. S.: C-Reactive Protein in Rheumatic Fever. Lancet **2:** 558 (Sept. 20), 1952.

The test for C-reactive protein used by the author was a ring precipitation test produced by layering 1 in 10,000 dilution of C polysaccharide over undiluted serum. Results were expressed quantitively from +4 downwards. Confusion with precipitation due to C-polysaccharide antibody was avoided by retesting with citrated serum; when antibody is responsible for the precipitation, the test remains positive in the absence of calcium. The experience reported was limited to 13 cases of rheumatic fever. Positivity of the tests for C-reactive protein faithfully mirrored fluctuations in activity of the disease. The sedimentation rate frequently remained elevated for a time in early convalescence after the C-reactive protein test had reverted to negative. Salicylates resulted in "disappearance" of C-reactive protein. This worker is of the opinion that the type of test which uses antiserum specific for C-reactive protein is, because of its greater sensitivity, likely to be more helpful in establishing the existence of smoldering rheumatic activity.

McKusick

Fischel, E. E., Frank, C. W., and Ragan, C.: Observations on Treatment of Rheumatic Fever with Salicylate, ACTH and Cortisone. Medicine **31:** 331, (Dec.), 1952.

The authors emphasize the many variables of rheumatic fever which make it so difficult to establish rigid criteria for therapeutic effectiveness in management of the disease. They review some well-known publications on the subject and point out various shortcomings. Among these are the lack of agreement on criteria of rheumatic activity; comparisons of cases treated at different institutions and in different decades; and statistical analyses presented without elucidation of illustrative case histories. A surprising feature is the omission in otherwise well-controlled studies of a most significant factor, the duration of the disease before the start of therapy. The authors stress the great importance of considering not only the comparative approach of alternate cases, but also two other types of evaluation: first, observation of therapeutic effects in chronic active cases in which a relatively stable state of activity offers a good opportunity to evaluate changes produced by therapeutic agents; second, method employment of an intrinsic control equally applicable to acute and chronic cases, namely, the occurrence of a flare-up in signs of activity upon the premature withdrawal of treatment which had suppressed manifestations of activity. This rebound may be taken as evidence that the disease had persisted during the period of therapy and that the inflammatory manifestations were being controlled to some degree during treatment.

Nine illustrative cases are discussed in some detail, particularly with regard to the rebound phenomenon observed in most of them following premature withdrawal of salicylate, or significant reduction of dosage. Some evidence was seen to indicate that salicylate may affect inflammatory changes in extra-articular serosal membranes and even in the heart. Vagaries of the relationship of the P-R interval to salicylate and to hormonal therapy were noted. The value of prolonged administration of salicylate, even for many weeks or months after subsidence of signs of activity, rather than running the risk of rebound flare-ups is discussed and examples cited.

Enselberg

Levine, S., and Love, E.: Mitral Stenosis without Murmurs. Cardiologia **21:** 599 (Fasc. 4/5), 1952.

In about 5 to 10 per cent of all cases of mitral stenosis no apical diastolic murmur may be heard despite the presence of a marked and often incapacitating constriction of the mitral ostium. Nineteen such cases proven by autopsy were reviewed and the following additional signs were established as helpful in the diagnosis of the lesion: Accentuation of the first mitral and second pulmonic sound; a third sound in diastole without apparent other cause; broad and notched P waves and evidence of right ventricular hypertrophy in the electrocardiogram; x-ray evidence of left auricular and right ventricular enlargement and calcification of the mitral valve; the presence of auricular fibrillation in a patient with the past history of rheumatic fever; typical alterations of the cardiodynamics as revealed by catheterization. In exceptional instances exploratory operation may become necessary to establish the diagnosis.

Among the possible reasons which may account for the absence of the typical diastolic murmur were noted marked cardiac dilatation with auricular fibrillation, severe congestive failure with a large residual blood volume in the heart, pulmonary emphysema, obesity and other conditions with increased anterio-posterior diameter of the chest, and a maximal degree of mitral stenosis.

Pick

ROENTGENOLOGY

Zinsser, H. F., Jr., Schnabel, T. G., Jr., and Johnson, J.: Roentgenographic Localization of Descending Aorta. J. A. M. A. **150:** 1200 (Nov. 22), 1953.

The authors state that in their experience the Potts-Smith-Gibson operation, which produces a direct communication between the descending aorta and the pulmonary artery, is technically more suitable for infants than the Blalock procedure. Utilization of this operation demands a prior knowledge of the location of the descending aorta, since its position

determines the side of the operative approach. The use of barium and the use of an over-penetrated Bucky film delineating the trachea furnish indirect evidence but do not unmistakably locate the descending aorta. While angiocardiography is satisfactory, infants who require constant oxygen administration react poorly to such a diagnostic procedure. In order to combine simplicity and minimal risk, the authors ascertained the location of the descending aorta in a 4½ month old boy by inserting a small polyvinyl catheter into the aorta through a number 21 gauge needle placed in the femoral artery. By means of an opaque contrast material the polyvinyl catheter was rendered radio-opaque. X-ray studies then showed the descending aorta to be to the left of the spine and a successful Potts-Smith-Gibson operation was immediately performed.

KITCHELL

Wickbom, I.: Death Following Contrast Injection into the Thoracic Aorta. Acta radiol. **38:** 350 (Nov.), 1952.

A case is reported in which death followed thoracic aortography after percutaneous puncture of the aortic arch from above the right clavicle. There was a serious reaction to the contrast injection but none to the puncture. At autopsy there was no evident damage which could be attributed to the puncture. The author is of the opinion that the fatal outcome was due to the contrast medium which remained in the coronary arteries for at least seven seconds.

SCHWEDEL

Wickbom, I.: Thoracic Aortography after Direct Puncture of the Aorta from the Jugulum. Acta radiol. **38:** 343 (Nov.), 1952.

The author punctured the aorta directly from above the right clavicle just lateral to the common carotid artery with a needle 12–13 cm. long and an outer diameter of 1.8 mm. General anesthesia is preferred, but not absolutely necessary. Thirty to forty-four cc. of a 70 per cent organic iodide contrast substance were injected within three seconds; roentgenograms were taken serially and rapidly. Two of the eight patients developed mediastinal hematoma which subsided within two to seven days. One patient died on the following day of circulatory insufficiency. The quality of the opacified aortograms was excellent.

SCHWEDEL

Denstad, T.: Abdominal Aortography. Acta radiol. **38:** 187 (Sept.), 1952.

The author relates his experiences with 97 cases of abdominal aortography. He feels that the injection of 10 cc. of an 80 per cent sodium iodide solution is too irritating and painful and therefore employs 30 cc. of 70 per cent organic iodide. Local anesthesia is preferred to general, permitting the fully conscious patient to hold his breath during the injection. No serious complications were encountered in this series and a review of over 3000 cases in the literature indicated only one fatality due to this procedure.

The author regards the procedure as being valuable in demonstrating arterial anomalies, arteriosclerosis, aneurysms, aortic thrombosis, displacement of arteries by cysts and tumors, and the characteristic filling of small arteries within neoplasms.

SCHWEDEL

Greenberg, S. U., Rosenkrantz, J. A., and Berenbaum, S. L.: Prominence of the Left Midcardiac Segment in Thyrotoxicosis as Visualized by Roentgen Studies. Am. J. M. Sc. **224:** 559 (Nov.), 1952.

The records of 106 patients with thyrotoxicosis who were apparently free of cardiovascular disease were analyzed in order to determine the incidence of the roentgenologic finding of prominence of the left midcardiac segment. The grading of the change noted along the left heart border was based upon the degree of convexity found in the region from the aortic arch to the left ventricle. In one third of the patients, the normal concavity of this area was present. However, in two thirds, there was an increase in the prominence of the left midcardiac segment; this change was pronounced in 42 per cent of the patients. The authors state that no cause for this roentgenologic finding is apparent; nor is there any obvious reason for one third of the patients escaping this change. Several theoretic considerations are presented based upon the effect of thyrotoxicosis upon cardiovascular physiology.

SHUMAN

BOOK REVIEWS

Clinical Electrocardiography: A Textbook for Practitioners and Students. *Dr. Max Holzmann, Zurich. Translated by Douglas Robertson, M.A., D.M. (Oxon.), M.R.C.P. (London).* London, New York, Staples Press, 1952. 647 pages, 302 figures, 9 tables. $21.00.

Robertson has translated Holzmann's book into idiomatic English that is admirably lucid and as free of jargon as a scientific book that requires precise terms can be. This book not only covers adequately its title's entire subject but reveals an author who has clinical judgment that no electrocardiogram can corrupt.

After a brief discussion of the history and of the underlying anatomic and electrophysiologic principles of electrocardiography and of the apparatus used, an analysis is given of the normal electrocardiogram. Following Duchosal, all electrocardiographic leads are regarded as secondary abstractions of the vectorial concept. Here, more clarity would be achieved if electrocardiograms accompanied the diagrams (for example, fig. 44). This concept leads to the normal postural types that replace Wilson's concept of electrical positions.

Consideration of the abnormal electrocardiogram, after differentiation from artefacts, begins with a discussion of situs inversus, fixation of the heart and abnormal amplitudes. Holzmann thinks that differentiation can be made between left and right auricular disease and that defects in conduction within each chamber can be recognized. The reviewer thinks that insufficient evidence is presented to support these concepts. The clinician, however, emerges triumphant because Holzmann concludes that "only when the abnormal electroauriculogram is associated with an abnormal electro-ventriculogram or with a pathologic clinical condition, does it assume any practical value." The reviewer also thinks that the concept of arborization block is not adequately analyzed from a vectorial concept. T waves that are preterminally negative are sharply differentiated from terminally negative ones on a basis of a difference in duration of excitation of injured muscle. In succession, the author discusses abnormal ventricular excitation and axis deviation, and changes found in inflammatory, toxic, allergic, endocrine and avitaminotic states and during the exhibition of drugs.

Infarction and ischemia are treated at length. Holzmann believes that exercise tests should be graded according to the case and that "we should always be able to deduce supportive evidence for our interpretations and . . . not . . . exclude the possibility of coronary artery disease because of the absence of the reaction of ischemia."

After sections on pericarditis, pulmonary embolism autonomic and orthostatic influences, abnormal U waves and alternans, a monographic discussion of disorders of rhythm follows. This superb analysis is marred only by the discussion on quinidine, an inevitable result of the time lag between writing and publishing a book containing matter subject to change. Holzmann closes with sections on trauma, congenital heart disease, tumor, neuropathies and myopathies and the dying heart.

Holzmann writes: "The clinical value of an electrocardiographic tracing is by no means proportional to the intensity of its changes, and its practical significance may be gauged only when the special pathologic conditions concerned have been duly considered." Here, then, is an expert electrocardiographer who as an expert clinician knows that electrocardiography is but one method, of variable significance, in the total evaluation of an individual's health.

Robertson's translation is confidently recommended to all physicians who have use for the electrocardiogram.

LOUIS A. SOLOFF

Physiologic Therapy for Obstructive Vascular Disease. *Isaac Starr, M.D.* Modern Medical Monographs No. 6. New York, Grune & Stratton, 1953. 46 pages, 4 figures, 3 tables. $2.50.

This monograph is based on the George E. Brown Memorial Lecture presented by the author before the American Heart Association in 1952. Dr. Starr discusses his personal clinical research on patients with ischemia and, as would be expected, he stresses physiologic methods of treatment. He was one of the first to recognize the importance of not overheating the ischemic extremity. He recalls the use of the cutaneous histamine test for evaluating severe grades of ischemia. He points out the importance of cardiac output as well as the occurrence of generalized vasodilatation when vasodilator drugs are used in an attempt to increase blood flow to the extremities. The importance of care of the feet as a preventive measure and the value of holding the ischemic extremity lower than the rest of the body are emphasized. Dr. Starr agrees with most men who treat vascular patients that sympathectomy is of value in the development of collateral circulation. This monograph is in the Lewis tradition in stressing physiologic principles behind treatment, and helps in placing present conservative methods on a more solid basis.

MEYER NAIDE

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ASSOCIATION FELLOWSHIPS AND GRANTS

Applications for Research Fellowships and Established Investigatorships for the 1954–55 fiscal year must be received by Sept. 15, 1953. Applications for research grants-in-aid may be filed up to Dec. 1, 1953. Information and forms may be obtained from the Association's Medical Director.

SECOND INTERNATIONAL CONGRESS OF CARDIOLOGY

Membership in the Second International Congress of Cardiology, which will be held in Washington, D. C., Sept. 12 through 15, 1954, will be open to all members of affiliated national cardiological societies and associations throughout the world, according to an announcement by L. Whittington Gorham, M.D., Secretary-General. Membership will also be open to other physicians and scientific workers of comparable status residing in countries where there are as yet no national cardiological societies. Nonmembers will be permitted to attend the Scientific Sessions by special invitation.

Those desiring to present papers at the Scientific Sessions must submit titles of papers with abstracts of not over 200 words in English, French and Spanish (and if desired, also in one other language) to the Secretaries of their national cardiological societies. These officers will forward to the Secretary-General only those papers which have been approved by the executive committee of each national society. From countries where there are no cardiological societies, titles and abstracts must be sent to the following:

Europe: Professor F. Van Dooren, Secretary-General, Pan European Cardiological Society, 800 rue Mercelis, Brussels, Belgium;

Latin America: Professor Ignacio Chavez, Director, National Institute of Cardiology, Mexico City, Mexico;

All other areas: L. W. Gorham, M.D., Secretary-General, Second International Congress of Cardiology, 44 East 23rd Street, New York 10, N. Y.

Both abstracts and translations must be submitted in duplicate, typed double-spaced, with wide margins, and on one side of the sheet only. All titles and abstracts must arrive in the United States on or before Feb. 1, 1954. Final selection will be made by the Program Committee on the basis of providing a well-coordinated, balanced program. It is planned to have members from abroad present nearly all of the papers at the Congress, while members from the U. S. will make their presentations chiefly at the Scientific Sessions of the American Heart Association which will be held in Washington immediately after the Congress, on Sept. 16 through 18, 1954.

Registration fees for the Congress will be: Members, $25.00; Associate Members (wives and children) $10.00 per person, payable in dollars or draft on U. S. banks.

SCIENTIFIC PROGRAM OF SECTION ON CLINICAL CARDIOLOGY

The Section on Clinical Cardiology of the American Heart Association will sponsor a two-day scientific program at the Conrad Hilton Hotel in Chicago on April 3 and 4, 1954. This program will constitute a portion of the Annual Meeting of the American Heart Association and will immediately precede the Annual Sessions of the American College of Physicians.

The meeting will be open to all members of the medical profession. Wright R. Adams, M.D., Chicago, is Chairman of the Program Committee. Members of the American Heart Association who wish to present papers should send a 250 to 300 word abstract of the proposed paper to Charles D. Marple, M.D., Medical Director, American Heart Association, 44 East 23rd Street, New York 10, New York. *All papers should be on subjects of distinct clinical interest. The deadline for the receipt of abstracts is Jan. 1, 1954.*

COMMITTEES

A new Committee on Auscultatory Phenomena (Tape Recordings) has been appointed by the Scientific Council of the Association. J. Scott Butterworth, M.D., New York University Post-Graduate Medical School, has been named Chairman.

The Committee on Stress and Trauma of the Scientific Council has been reactivated, with Paul D. White, M.D., Boston, as Chairman.

COMMUNITY SERVICE AND EDUCATION

William A. Brumfield, Jr., M.D., Syracuse, N. Y., has been designated Chairman of the Executive Committee of the Association's newly established Council on Community Service and Education. Dr. Brumfield is Professor and Chairman of the Department of Preventive Medicine, State University Medical Center, Syracuse, N. Y.

Mrs. Julie Perrin, a Board member of the American Social Hygiene Association, has joined the staff of the Association's Community Service and Education Division as a Program Consultant for Heart Associations in eleven Pacific Coast and Rocky Mountain States. Her headquarters will be in San Francisco.

NEW AFFILIATE

The Tennessee Heart Association has been organized as a direct affiliate of the American Heart Association. Four existing affiliates, in Chattanooga, East Tennessee, Memphis and Middle Tennessee, have become chapters of the Tennessee Heart Association, which will maintain headquarters in Nashville.

SECOND BLAKESLEE AWARD

Entries are now being received for the Association's second annual $1,000 Howard W. Blakeslee Award for outstanding scientific reporting in the cardiovascular field. Named for the late Science Editor of the Associated Press, the award is presented annually to the individual whose creative efforts in any medium of mass communication—including newspapers, magazines, radio, television, films or books—are judged to have contributed most to public understanding of heart and circulatory diseases.

Entries are judged on the basis of their accuracy and significance; on the skill and originality with which advances in research and in the treatment, care and prevention of cardiovascular disease are translated into educational material of interest and value to the general public; and on the ability of the entrant to project a positive and hopeful viewpoint toward problems of the heart and circulation.

To be eligible for the second Award, material must have been published or produced during the 1953 calendar year. All entries must be received or postmarked by Jan. 15, 1954. The winner will be announced at the Association's Annual Meeting, to be held in Chicago in April 1954. Requests for entry blanks or additional information may be addressed to the Chairman, Managing Committee, Howard W. Blakeslee Award, American Heart Association, 44 East 23rd Street, New York 10.

RECENT PUBLICATIONS

The following recent publications of particular interest in the cardiovascular field are available from the Association or from affiliated Heart Associations:

Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Blood Vessels. A completely revised and greatly expanded Fifth Edition of this standard reference work has been prepared by the Criteria Committee of the New York Heart Association. It introduces some entirely new concepts and viewpoints developed in the last ten years and for the first time includes a section on diseases of the peripheral vessels. The book is published by the New York Heart Association and is distributed

by the American Heart Association. ($4.95, clothbound.)

Films in the Cardiovascular Diseases: Survey, Analysis and Conclusions, by David S. Ruhe, M.D., New York, and his associates of the Medical Audio-Visual Institute of the Association of American Medical Colleges, assisted by panels of cardiologists. The volume reviews 62 available films and lists 118 additional films in the cardiovascular field. It is directed to those interested in or concerned with using such films in teaching. ($1.50, paper-bound; $2.00 clothbound.)

Proceedings of the Annual Meeting, Council for High Blood Pressure Research of the American Heart Association, 1952. Six scientific papers reviewing original investigative work in this field are included in this monograph, as well as a number of informal addresses to laymen by physicians prominent in activities of the Association. ($1.75, paper-bound.)

REGISTRY OF CARDIOVASCULAR PATHOLOGY

Wallace M. Yater, M.D., Washington, D. C., has been reappointed Chairman of the Advisory Committee to the Registry of Cardiovascular Pathology for the fiscal year 1953–54. The Registry of Cardiovascular Pathology is a division of the American Registry of Pathology, a department within the Armed Forces Institute of Pathology. It is under the auspices of the National Research Council and is sponsored by the American Heart Association.

The Registry of Cardiovascular Pathology maintains a permanent file of contributed gross specimens, tissue blocks and microscopic slides, correlated with clinical histories, electrocardiograms and x-ray films. As of Dec. 31, 1952, 792 cases had been contributed to the Registry. They included: neoplasms, 26; collagen disease, 149; endocarditis, 174; malformations, 419; miscellaneous, 13; diagnosis in more than one series, 11.

Sets of teaching material, such as lantern slides and microscopic slides, are being prepared by the Registry. When completed, they will be made available on loan to interested physicians.

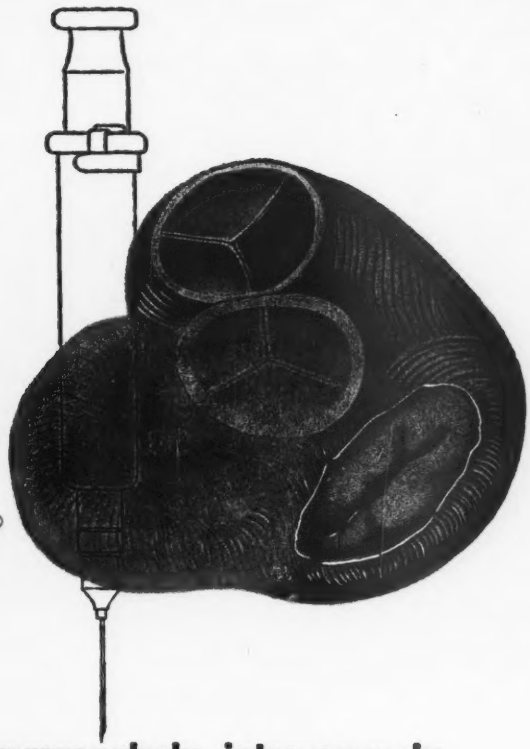
MEETINGS

Oct. 6–9: American Academy of Pediatrics, annual meeting, Municipal Auditorium, Miami, Fla. E. H. Christopherson, M.D., Executive Secretary, 610 Church Street, Evanston, Ill.

Oct. 12–16: La Rabida Sanitarium, Chicago, first annual institute on rheumatic fever. For additional information, apply to Institute, La Rabida Sanitarium, East 65th Street and South Shore Drive, Chicago 49.

Oct. 29: American Federation for Clinical Research, Midwestern Section, Annual Meeting, Congress Hotel, Chicago. Abstracts not exceeding 250 words, in triplicate, should be sent by Sept. 15 to Robert W. Schneider, M.D., Cleveland Clinic, 2020 East 93rd Street, Cleveland 6.

Nov. 1–2: American Society for the Study of Arteriosclerosis; Hotel Knickerbocker, Chicago. Louis N. Katz, M.D., Program Chairman, Michael Reese Hospital, Chicago 16.



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*Marsh, R.; Greiner, T.; Gold, H.; Mathes, S.; Palumbo, F.; Warshaw, L., and Weaver, J.: New England J. Med. 247:593 (Oct. 16) 1952.

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Circulation
A JOURNAL of the AMERICAN HEART ASSOCIATION
SEPTEMBER 1953
VOL. VIII NO. 3

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